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We are developing a drug-dispensing field dermal dressing. The dermal dressing, which can be easily applied by an untrained person, contains antimicrobials to prevent bacterial infection. The medicated dermal dressing is made of an ultra-fast curing polyurethane oligomer which is designed to cure at room temperture and delivers drugs on a controlled, sustained and highly reproducible basis.					
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FOREWORD

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In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

Kunt N Dasse ////il PI Signature Date

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INTRODUCTION

This report summarizes research conducted over the final year of the contract directed toward developing a second generation Antimicrobial Dermal Dressing (ADD). The dressing is a trilaminate composed of an outer medical grade polyurethane fabric, an acrylicbased pressure sensitive adhesive, and an antimicrobial impregnated polyurethane film which serves as a controlled drug release layer. The objectives in developing this new technology have been to create a dressing that is:

- (1) easily applied under adverse climatic conditions,
- (2) highly compliant and abrasion resistant, and
- (3) allows controlled release of antimicrobial agents over a
 72 hour period against a variety of specific microbial organisms.

The new dressing must be capable of incorporating sensitive antimicrobial agents and releasing them in a controlled fashion when in contact with the wound. This has been made possible by developing a room temperature, rapid ultraviolet (UV) curable liquid polyurethane oligomer. The liquid mixture of urethane and drugs is cured under UV lights and the resultant monolithic film provides controlled release of the agents when placed on the wound. This targeted drug delivery minimizes many of the inherent problems associated with conventional systemic drug delivery. The focus of the research over the third contract year has been to fabricate two types of dressings incorporating:

- (1) chlorhexidine gluconate, and
- (2) silver sulfadiazine coupled with a second synergistic antimicrobial agent.

Successful completion of the proposed tasks has involved manufacturing the base oligomer, developing reliable fabrication methods, establishing analytical methods to measure the antimicrobial agents, monitoring the elution kinetics and optimizing drug release. Accelerated shelf stability studies were also initiated. USAIDR assumed responsibility for in vivo evaluation of the technology.

This work has resulted in the development of new techniques for drug analyses, improved fabrication methods for sustained release and offers the possibility of enhanced wound healing. Work in the latter portion of the year was devoted to manufacturing and monitoring larger quantities of dressings for shelf stability studies. The following report provides a detailed description of the activities carried out in the performance of this program.

PROGRAM STATUS

The Antimicrobial Dermal Dressing (ADD) under development by Thermedics Inc. according to the terms of the USAIDR research contract DAMD17-88-C-8012 has been shown to be effective. Testing of two formulations was associated with excellent resultr in vivo when employed prophylactically on inoculated wounds in gainea pigs.

The first test was carried out on a Chlorhexidine Gluconate dressing, and was found to be highly effective against <u>Strep.</u> <u>pyogenes</u>, <u>Staph. aureus</u> and <u>P. aeruginosa</u> under the stringent conditions required by USAIDR. The second test of a Chlorhexidine Gluconate - Silver Sulfadiazine ADD, which is expected to be effective against <u>Candida albicans</u>, was also effective against <u>Staph. aureus</u> and <u>P. aeruginosa</u>. Both of these dressings are currently undergoing accelerated storage stability tests. The start of the storage tests were contingent upon being able to package the dressings in hermetically sealable envelopes. This requirement dictated the sterilization of the product by radiation methods. The irradiation method chosen was Electron Beam; this method showed no tendency to degrade the product.

All tasks are either completed, underway or should be completed by program end.

WORK TO DATE

TASK I

Task I required the preparation of the vinyl terminated silicone oligomer for Year 3 studies. All the ADD's fabricated during Year 3 of the contract were prepared from a single lot of oligomer.

TASK II

4

Task II called for the preparation of 200 sterile placebo dressings for FY90 User Test. These dressings were fabricated and prepared for delivery to USAIDR.

TASKS III AND IV

Tasks III and IV focussed on optimizing the formulation of the chlorhexidine gluconate dressing. Fabrication of the initial chlorhexidine gluconate dressings was completed by the end of Year 2 (Tasks VIII & IX). An increase in the amount of drug eluted was achieved by the modification of the excipients used in the formulation (1). This, as well as two additional test formulations was submitted to USAIDR for in vivo studies on guinea pigs. Following evaluation, the two final formulations of the ADD's were submitted for testing making a total of five (5) formulations

evaluated by USAIDR.

A. In Vitro Release Kinetics of Chlorhexidine Gluconate ADD's

The initial chlorhexidine gluconate ADD submitted for in vivo testing showed excellent bacterio*static* activity. However, it was subsequently learned that modification of the excipients further increased the release of drug from the matrix, with potential bacterio*cidal* activity. Figure 1 compares the in vitro release rates of formulation 1 with that of formulation 2, incorporating the different excipients.

The total drug content per unit area was shown to be altered by changing the thickness of the dressing. However, as was demonstrated in the animal trials, the 6 mil dressing (Formulation 2) was as effective as the 20 mil dressing (Formulation 3). Two factors limiting maximal thickness of the dressing relate to the flexibility of the ADD and the decrease in the percent elution of the total drug loading. To test flexibility, user tests were conducted with a maximum thickness dressing (20 mil) possible, worn on elbows and wrists. These dressings were found to conform to the uneven contours of the body, and remain adherent for periods up to 3 days. These dressings were also shown to be effective in parallel in vivo trials. However, to reduce cost, while maintaining efficacy, an optimal thickness had to be determined. The objective of this effort was to reduce the thickness to less than 20 mils,

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thereby lowering the amount of drug and cost, while maintaining efficacy and handling characteristics. Accordingly, the fourth and fifth formulations incorporating chlorhexidine gluconate, that were submitted for in vivo evaluation were 16 and 12 mils, respectively. All formulations submitted to USAIDR for in vivo trials are summarized in Table I. Figure 2 shows in vitro release kinetics associated with the four formulations of different thicknesses. While significant differences in the kinetics were observed in increasing the thickness of the ADD from 6 - 16 mils, no apparent difference was seen from 16 to 20 mils.

USAIDR Sub.No	o. Qty	Weight Ratio Drug: <u>Excipient</u> :Matrix	Thickness
Formulation 1	L 45	30: <u>30</u> :40	6 mils
Formulation 2	2 45	30: <u>6:24</u> :40	6 mils
Formulation 3	3 45	30: <u>6:24</u> :40	20 mils
Formulation 4	45	30: <u>6:24</u> :40	16 mils
Formulation 5	5 45	30: <u>6:24</u> :40	12 mils

Table I. Formulations Submitted to USAIDR Under Task IV.

Excipients: Propylene glycol 30 parts; Propylene glycol 6 parts and PEG 300 24 parts.

4 Э5 3 Cumulative Release mcg/cm2 (Thousands) 2.5 2 1 5 f 1 05 ٥ 20 40 ō Time in Hours Formulation 1 o Formulation 2

Figure 1. Comparison of the Release Rates of 30% Loaded Chlorhexidine Gluconate ADD's With Different Excipients (Formulation 1 contains 30% propylene glycol as the excipient; Formulation 2 contains 6% propylene glycol and 24% PEG 300).

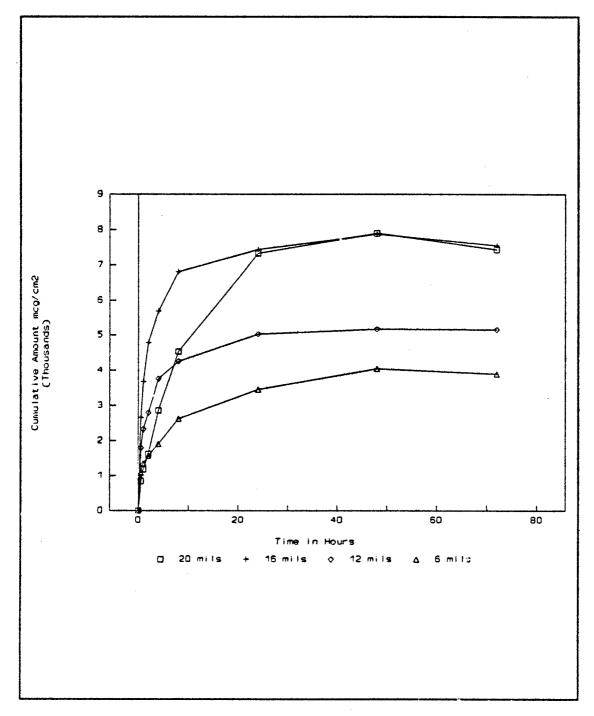


Figure 2. Comparison of the Release Rates of 30% Loaded Chlorhexidine Gluconate ADD's With Different Thicknesses (Excipient Blend 6:24 Propylene glycol to PEG 300).

B. Summary of Animal Test Results

The in vivo tests of the ADD's containing chlorhexidine gluconate were conducted at the laboratory facilities of USAIDR, in Maryland. Five different formulations of chlorhexidine ADD's were tested on inoculated guinea pigs and the results are summarized in Table II. Each dressing was evaluated utilizing the prophylactic protocol. Utilizing the prophylactic protocol, a wound was created, inoculated and the dressing applied immediately (2). The results described in Table II are those obtained utilizing the quantitative assay. Based on these results, formulations 2, 3, 4 and 5 incorporating the same excipient ratio (6:24 parts propylene glycol to PEG 300) were as effective as formulation 1 containing 30 parts of propylene glycol. However, these formulations were easier to fabricate compared to formulation 1. The thicker dressings, formulation 3 (20 mils), 4 (16 mils) and 5 (12 mils) also had superior handling characteristics compared to formulation 2 (6 mils).

USAIDR in vivo results showed that the 30% chlorhexidine gluconate formulations were 100% effective prophylactically. Formulation 5 demonstrated optimal balance between cost and handling characteristics and was chosen for the accelerated stability testing under Task VI.

USAIDR Gp #	N	None	Infec Subclinical	ction Clinical	
Placebo	4			4	
Formulation 1	6	4	2	0	
Formulation 2	7	4	3	0	
Formulation 3	6	5	1	0	
Formulation 4	5	5	. =	-	
Formulation 5	5	5	-	-	
Formulation 1 = 30% of Propylene				D, contair	ing
Formulation 2 = propylene glycol				ADD, with	6%
Formulation 3 = propylene glycol				ADD, with	6*
Formulation 4 = propylene glycol				ADD, with	6%
Formulation 5 = propylene glycol				ADD, with	6%

Table II. Summary of USAIDR In Vivo Tests - Biopsy Results.

TASKS V AND VI

Tasks V and VI included the fabrication, delivery and accelerated storage stability tests for sterilized chlorhexidine gluconate ADD's. The work statement called for 200 sterile ADD's to be delivered to USAIDR, along with 100 placebos for in vivo tests under Task V. Also an additional 100 ADD's were to be delivered for demonstration purposes. All ADD's had to be manufactured from the same lot as those tested for shelf stability under Task VI. The minimal number of ADD's required under these combined tasks was over 500.

The dressings submitted to USAIDR to this juncture in the program had been sterilized utilizing ethylene oxide. This method was shown to be effective and suitable for materials packaged in heat sealable, permeable pouches. Also, ethylene oxide sterilization permitted rapid processing for screening tests. However, ethylene oxide is a contact sterilant and is not effective on devices packaged in moisture resistant packages. The wound dressings prior to shelf stability testing were required to be packaged in moisture resistant aluminum pouches. Hence ethylene oxide was not the recommended method of terminal sterilization.

A. Effects of Sterilization

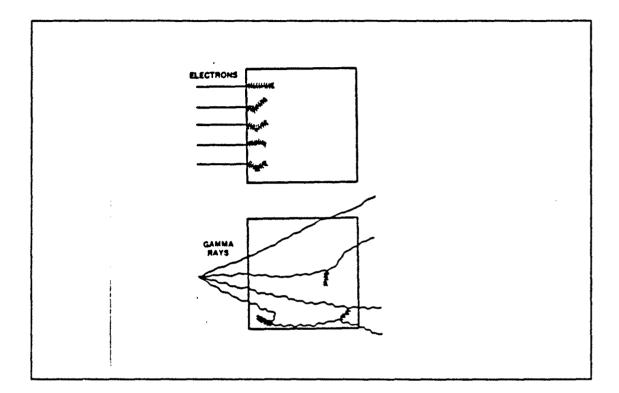
Ionizing radiation is a popular and established industrial process for the terminal sterilization of medical devices. The principle advantage of using ionization techniques is that the dressings can be sterilized in hermetically sealed aluminum pouches. Moreover, ionization techniques are generally simpler leaving no residuals and require no post-sterilization treatment.

There are two types of ionizing radiation:

- (a) electromagnetic radiation which includes gamma rays and X-rays, and
- (b) particulate radiation which includes beta and alpha particles.

Both types of radiation produce bactericidal effects through the interaction of high energy electrons and the substrate. In the former, gamma radiation, the high energy electrons are produced by the interaction of gamma rays with the atomic electrons of the substrate. In the latter, beta particles (electrons) are delivered from an external source in predetermined doses. In both of these types of radiation, it is the high energy electrons which produce chemical changes in the target leading to the destruction of microorganisms (3, 4). The degree of ionization achieved in any device is directly related to the amount of radiation absorbed. When applied to packaged products, both gamma rays as well as electron particles effectively penetrate the packaging and

sterilize the product. However, the degree of penetration, as well as the degree of ionization due to gamma radiation, far exceeds that of electron beam radiation (Figure 3).





Gamma radiation, due to its penetrative, energy transmittance properties, has the potential to cause undesirable side effects with many polymers (5, 6). Electron beam on the other hand, utilizes an external finite dose of electrons. The degree of penetration and ionization within the substrate is controlled by the dose. This method is less likely to cause deleterious effects on polymer networks such as degradation or crosslinking (7), is highly effective, and widely used for terminal sterilization of hermetically packaged devices. Based on the known mechanisms of each of these forms of sterilization, gamma radiation is less attractive as a means of sterilizing the ADD because it may have a greater effect on the polymer/drug interaction compared to electron beam methods.

The effect of these sterilization techniques, i.e. ethylene oxide, gamma and electron beam radiation, on the release kinetics of the wound dressings were compared using in vitro diffusion methods. Initial tests performed on the packaged ADDs' showed that the elution kinetics of dressings subjected to gamma sterilization exhibited a lower release rate, and reduced the total amount of drug eluted from the polymeric matrix (Figure 4). The dressings subjected to electron beam radiation, on the other hand, exhibited release kinetics comparable to ADDs' subjected to ethylene oxide, as illustrated in figure 5.

Based on the elution kinetics and preliminary results in animals, it was recommended that the dressings be packaged in hermetically sealed aluminum pouches followed by sterilization utilizing electron beam radiation methods.

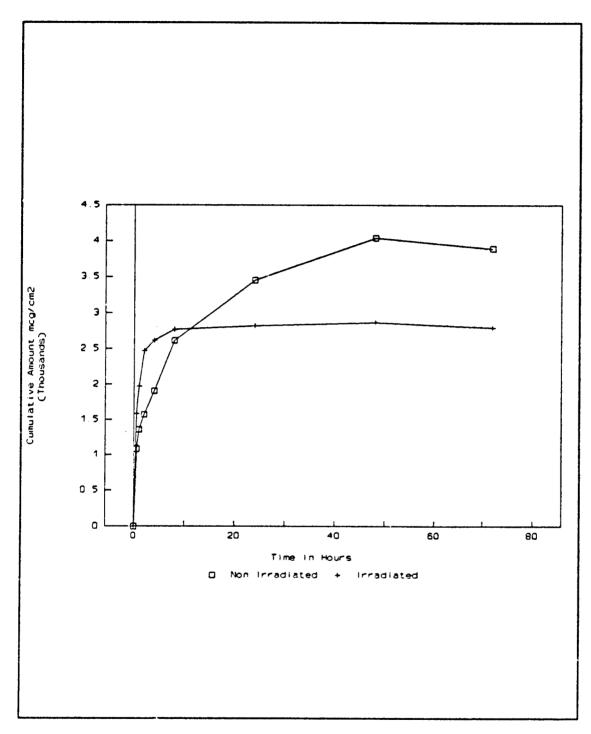


Figure 4. Effect of Gamma Radiation on a 6 Mil Thick Chlorhexidine Gluconate ADD (Note the reduction in drug release in the gamma irradiated sample).

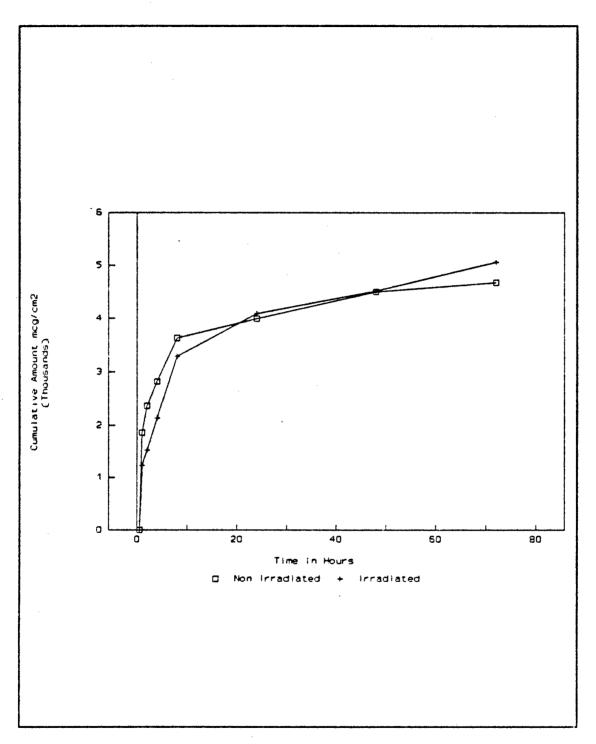


Figure 5. Effect of Electron Beam Radiation on a 12 Mil Thick Chlorhexidine Gluconate ADD.

B. Fabrication of Chlerhexidine Gluconate ADD's for Accelerated Shelf Stability Studies

All prior batches manufactured at Thermedics for delivery to USAIDR, were made utilizing 150 grams of material which yielded 100 to 150 ADD's. The requirements of Tasks V and VI called for the scaling up of the batch sizes 3 to 4 times. A pilot batch was manufactured using a laboratory scale Hockmeyer mixer. The excipients were first mixed and the lyophilized chlorhexidine gluconate slowly dispersed. The oligomer was then added into the drug-excipient mixture. The drug loaded oligomer was cured under UV lights. The resultant roll stock was then die cut, placed on Spandra⁸ and the fabrication completed. The final dressings were sealed in aluminum pouches and sterilized by electron beam irradiation.

Five hundred and forty (540) chlorhexidine gluconate ADD's were fabricated and sterilized. Two hundred 1.5 x 1.5 inch ADD's were delivered to USAIDR, along with 100 placebos for in vivo animal testing. An additional one hundred 1 x 1 inch ADD's were also delivered for demonstration purposes. The remaining ADD's were set aside for shelf stability studies.

C. Shelf Stability Studies

The chlorhexidine gluconate ADD's were subjected to a battery of quality control tests. The elution kinetics were recorded documenting the initial time point (t = 0) for the accelerated shelf stability. The baseline release profile of these ADD's is shown in figure 6. The dressings exhibited effective results when subjected to microbiological zone of inhibition and sterility tests; these results along with the certificate of analysis, are appended (Appendix I).

Careford States and Careford

The ADD's were subjected to various temperatures for the accelerated shelf stability studies. Forty-eight ADD's were tested under five conditions specified below:

- (1) 45⁰ C, 90% R.H
- (2) 38⁰ C, 90% R.H,
- (3) Room Temperature,
- (4) 23° C, under water,
- $(5) 40^0$ C.

The stability of chlorhexidine ADD's is being determined using two methods:

- analyzing the drug for the presence of the degradation product, and
- measuring the maximum amount of drug eluted from the ADD's over 72 hours.

The major decomposition product of chlorhexidine gluconate is p-chloroaniline (PCA). A concentration of five hundred micrograms per milliliter (mcg/ml) of PCA is considered a safe biological level in animals (8). This value corresponds to a 25% degradation of chlorhexidine gluconate. A tenth of this value was selected as the maximum allowable concentration of PCA: i.e. 50 mcg/ml, which relates to 2.5% PCA or a 97.5% stable product. The assay methodology adopted in our laboratory for chlorhexidine analysis has a sensitivity of less than 10 mcg/ml (<10 mg) of PCA. The accelerated stability tests conducted until now show that chlorhexidine gluconate is stable when stored at 45° C for two months. Results of the assay show p-chloroaniline to be below detectable limits; figure 7 represents a chromatogram depicting this result. Figure 8 represents a chromatogram of a 1000 mcg/ml chlorhexidine gluconate standard spiked with p-chloroaniline. A comparison of these two chromatograms confirms that chlorhexidine gluconate stored at 45° C for two months does not exhibit any detectable degradation products.

The second method for determining storage stability involves an analysis of elution data acquired from ADD's removed from each of the storage conditions. The tabulated results and elution curves for these five conditions (-40° C, 23° C under water, ambient, 38° C and 45° C) are summarized in Table III and figure 9. Figure 10 lists data obtained for these samples compared with those at t = 0 revealing no significant change in elution rates. This series of 6 curves was generated from 1 data point for each time period. Therefore, it was decided to use a "paired t-test", to compare the 2 extremes; -40° C and 45° C. The statistical results summarized below indicate there is no significant decrease in drug elution at the two month period.

Cumulative Amount Chlorhexidine Gluconate (mcg/cm²)						
Time (Hours)	t = 0	45°C	38ºC	23°c water	RT	-40ºC
0	0	0	0	0	0	0
0.5	1054	945	858	1173	1069	1216
1	1442	1427	1.304	1528	1546	1670
2	1935	1507	1683	1950	1785	2037
4	2925	2067	2530	3028	2661	3104
8	3745	2808	3380	4134	3724	4110
24	4300	3765	4037	4823	4639	4616
48	4647	3955	4021	4940	4843	4957
72	4501	4173	4056	5014	4928	4642

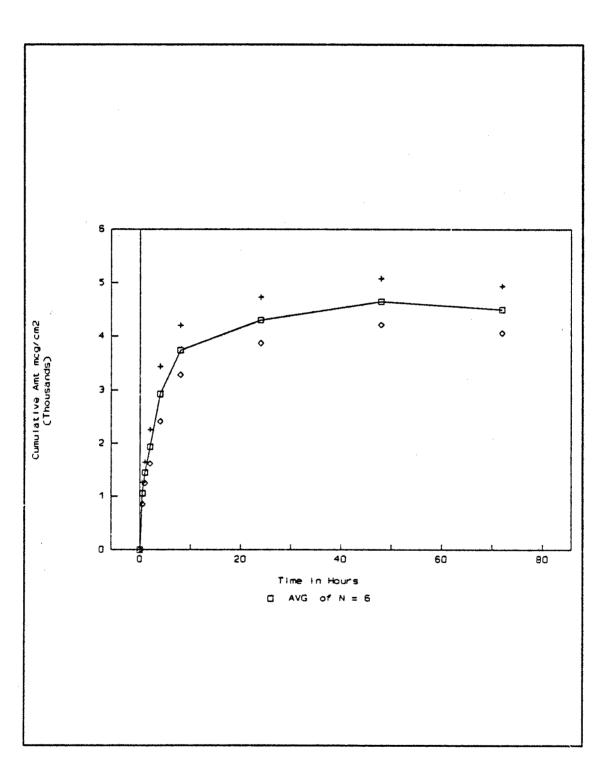
Table III. Results of Two Month Shelf Stability

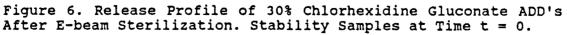
Table IV. Results of "Paired t-test" Performed on Samples Stored Under Extreme Conditions.

Two Sample Analysis Results

Sample Statistics : No. of Obs. Average Variance Std. Dev. Median	9 2294.11 2 2.1528E6 2	3.15158E6 1775.27	18 2611.06 2.65219E6 1628.56
Conf. Interval for Ratio of Variance (Equal Vars.) Sample 1 - Sample (Unequal Vars.) Sample 1 - Sample	2 -2261.	76 993.984	
Conf. Interval for Ratio of Varianc Sample 1 v Sample 2	es :	0 per	rcent
<u>Hypothesis Test for HO</u> : Diff = 0 vs Alt: NE Sig. at Alpha = 0.05	Level = 0.4	421122	= −0.82569

Sample 1 = 45° C Sample 2 = -40° C





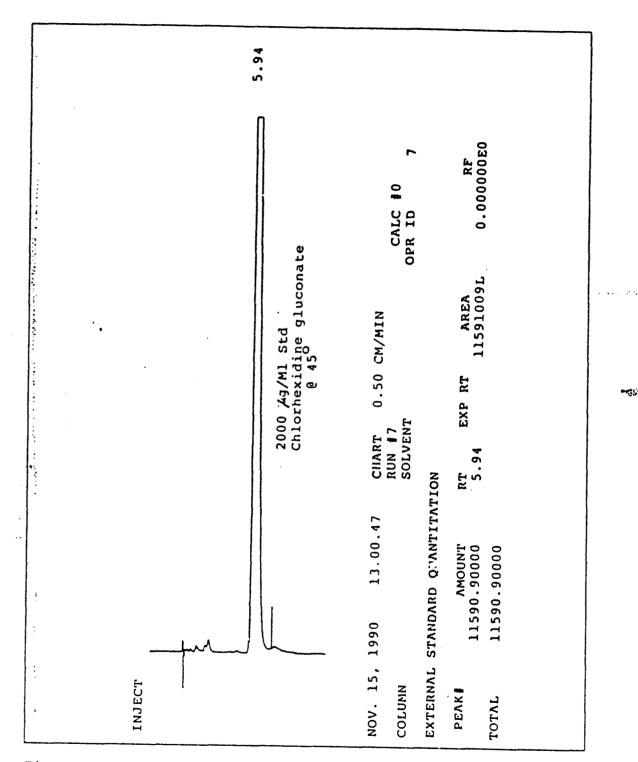
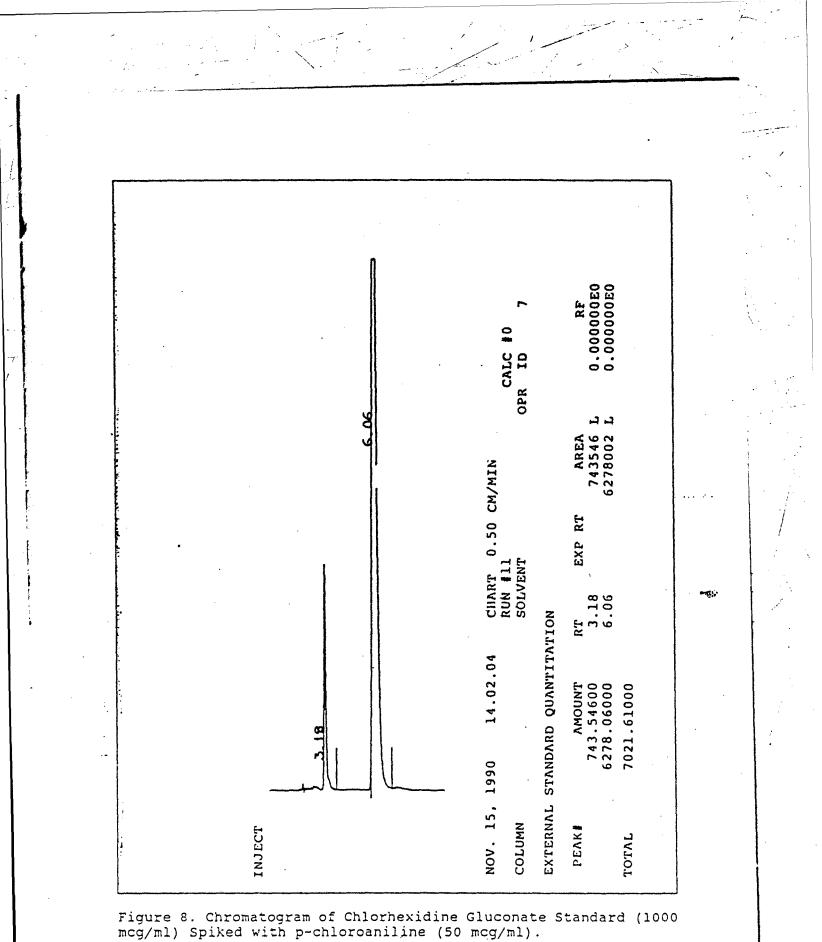


Figure 7. Chromatogram of Lyophilized Chlorhexidine Gluconate Stored at 45° C for Two Months.





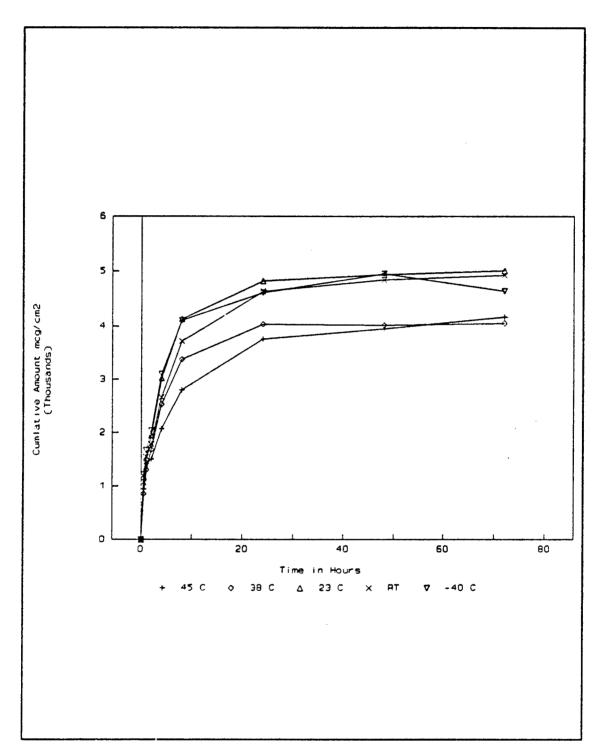


Figure 9. Elution Curves of 'Iwo Month Stability Samples of Chlorhexidine Gluconate ADD's.

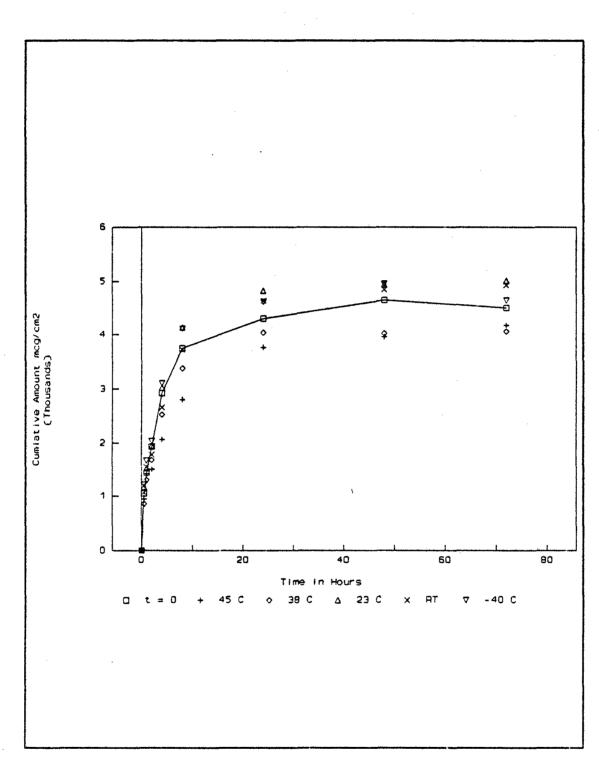


Figure 10. Comparison of the Elution Curves of the Chlorhexidine Gluconate ADD's at Time Periods, t = 0 & t = 2 Months.

TASK VII

The second medicated antimicrobial dermal dressing to be developed had to be effective against a broad spectrum of bacteria: <u>Staphylococcus aureus</u>, <u>Pseudomonas aeruginosa</u>, <u>Streptococcus</u> <u>pyogenes</u>, and fungi such as <u>Trichophyton</u> species, <u>Epidermophyton</u> species and <u>Candida albicans</u>. Many antimicrobials were screened for their spectrum of activity to find suitable candidates for incorporation into the UV cure polymer matrix. The most promising candidate, silver sulfadiazine was fabricated into ADD's for in vivo evaluation.

A. Preparation of Formulations Incorporating Photo Opaque Drugs

Initial trials based on microbiological tests, using a two percent silver sulfadiazine loading showed that a higher concentration was necessary in order to be effective. However, incorporation of larger amounts of drug prevented the polymer from curing into a film. Photo opaque powdered drugs such as silver sulfadiazine and nystatin inhibit or interfere with the polymerization of the oligomer by blocking the UV energy needed to dissociate the photoinitiator into free radicals. Comparison of the UV absorbance spectrum for Irgacure 651 and Silver sulfadiazine (Figures 11 and 12) showed that these two compounds had similar maximum absorbance peaks at 260 nanometers.

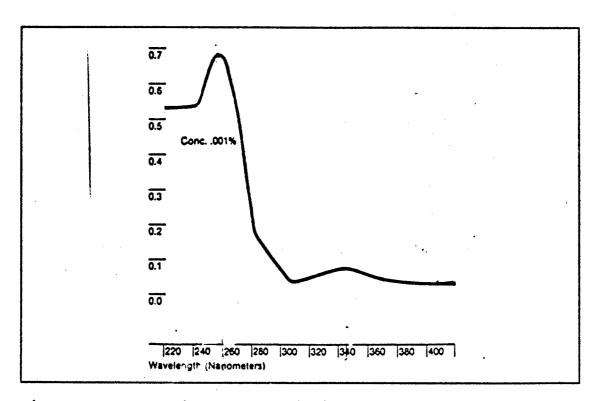


Figure 11. Absorption Characteristics of Irgacure 651.

It became necessary to investigate the use of a photoinitiator which dissociated through the absorption of a longer wavelength energy incorporating photo-opaque for drugs. One such photoinitiator is camphorquinone, which has been medically accepted in the dental industry for curing acrylic fillings (9). This compound has a maximum absorption wavelength of 460 nanometers, well above the interference levels of silver sulfadiazine. Various concentrations of silver sulfadiazine were incorporated into the polymer using the new photoinitiator. Cured films containing silver sulfadiazine showed that drug loadings up to 30% were possible employing this photoinitiator.

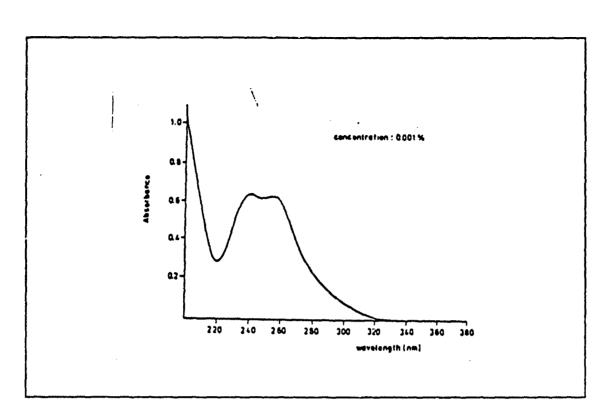


Figure 12. UV Spectrum of Silver Sulfadiazine.

Sample dressings containing nystatin exhibited the same curing problem as the silver sulfadiazine dressings. The inability to cure was eliminated by using the long wave length photoinitiator, camphorquinone. The use of this initiator permitted the fabrication of test sheets for Task XI (Year 2) containing high levels (up to 30%) of nystatin and silver sulfadiazine.

B. Drug Formulation Screening Tests

The activity of antimicrobials was evaluated using plate assay techniques to measure the inhibitory effect of candidate drugs on microorganisms. Utilization of microbiological methods detects a change in antimicrobial activity that may go undetected using standard chemical methods. The plate assay technique depends upon diffusion of a test antibiotic from a saturated disc, through a solidified agar layer in the petri dish, so that growth of the target microorganism is prevented entirely in a circular area (zone) around the disc containing a solution of the antimicrobial. In Task XI (Year 2), assay plates were prepared by pouring a molten mixture, 1 to 10 ratio of Staphylococcus aureus, Pseudomonas aeruginosa and Streptococcus pyogenes inoculum with Trypticase Soy Agar (TSA), or Candida albicans and Trichophytons inoculum with Sabaurouds Dextrose Agar (SDA), into petri dishes and allowing it to harden. The TSA plates were incubated at 30 - 35°C for 72 hours and the SDA plates at $20 - 25^{\circ}C$ for 5 days. This procedure was repeated for each test formulation and the controls. Attempts to screen a sixth organism, Epidermophytons failed. This microorganism has an incubation period of 22 - 24 days, which is well beyond the effective duration of activity (72 hours) of the fabricated dressings.

Fourteen different formulations incorporating Silver sulfadiazine, Clindamycin phosphate, Gentamicin sulfate,

Chlorhexidine gluconate or Nystatin, either alone or in combination with one another were tested (Table V). Twelve of these test samples were formulated to a 30 percent loading; i.e. 30 milligrams of drug per 100 milligram patch. The formulation incorporating three antimicrobials; i.e. clindamycin, gentamicin and silver sulfadiazine, was selectively tested for activity against gram negative and gram positive bacteria and fungi. The most promising test results are reported in Table VI.

Antimicrobial	Concentration by weight (%)
Chlorhexidine	30
Chlorhexidine [*]	30
Chlorhexidine	33
Chlorhexidine Nystatin	15 15
Chlorhexidine Nystatin	20 10
Chlorhexidine Silver sulfadiazine	15 15
Chlorhexidine Silver sulfadiazine	10 20
Silver sulfadiazine	30
Silver sulfadiazine*) 10
Silver sulfadiazine Nystatin	20 10
Chlorhexidine Silver sulfadiazine Nystatin	10 10 10
Nystatin	30
Silver sulfadiazine**	2
Clindamycin phosphate Gentamicin sulfate Silver sulfadiazine	20 25 2

Table V. List of Formulations Tested Microbiologically.

* Irgacure 651 was used as the photoinitialor. * Silver sulfadiazine was incorporated in a hydrophilic cream.

Test Formulation	S.aureus	P.aerug	Test Org S.pyog C.		T.mentag
10% Chlor. 10% S.sulfa 10% Nystatin	+	+	+	+	+
15% Chlor. 15% Nystatin	÷	+	+	+	+
10% Chlor. 20% S.sulfa.	+	+	+	+	+
20% S.sulfa. 10% Nystatin	+	+	+	+	+
20% Clinda. 25% Genta. 2% S.sulfa.	+	+	N/A	+	N/A
The formulations promising results		here	are those	which	n showed

Table VI. Summary of Zone of Inhibition Tests.

TASK VIII

This task required the submission of five formulations to USAIDR for in vivo testing on guinea pigs. The five formulations reported in Table VI appeared equally effective against target organisms based on the zone of inhibition tests. Nystatin is primarily an antifungal agent and exhibits no antibacterial properties, whereas silver sulfadiazine exhibits both antifungal and antibacterial activity. Moreover, sulfadiazine has been shown to have synergistic properties in the presence of chlorhexidine (10). Results of the zone of inhibition screening test demonstrates the microbiological efficacy of this combination. Based on these observations, an initial formulation was prepared incorporating 20% silver sulfadiazine in combination with 10% chlorhexidine gluconate for in vivo testing.

The results of the in vivo test for this initial formulation indicated this choice was effective for prophylactic treatment. However, the dressings were not as effective when tested under therapeutic conditions. The incorporation of previously tested antibiotics was thought necessary to improve therapeutic efficacy. However, an in vitro test showed that combinations of gentamicin sulfate with chlorhexidine gluconate were chemically incompatible. Therefore, the remaining formulations submitted under Task VIII incorporated various combinations of silver sulfadiazine, chlorhexidine gluconate and clindamycin phosphate.

A. Formulations Submitted Under Task VIII.

Forty five dressings of five formulations were fabricated and submitted to USAIDR for in vivo tests on guinea pigs. The formulations consisted of:

- (1) 20% Silver sulfadiazine and 10% Chlorhexidine gluconate(B.N. 003281),
- (2) 20% Clindamycin phosphate and 10% Chlorhexidine gluconate(B.N. 007121),
- (3) 20% Silver sulfadiazine and 10% Clindamycin phosphate(B.N. 007131),
- (4) 10% Silver sulfadiazine, 10% Chlorhexidine gluconate and10% Clindamycin phosphate (B.N. 007132)
- and, (5) 12% Silver sulfadiazine, 10% Chlorhexidine gluconate and 12% Clindamycin phosphate (B.N. 009101).

The ADD's containing clindamycin phosphate and chlorhexidine gluconate (B.N. 007121) did not require any modification of the excipients to facilitate UV cure. However, the other three formulations containing silver sulfadiazine required alternative excipients. The use of alternative excipients was necessary because heterogenous immiscible phases formed while using the existing excipient which caused the mixture to separate at the knife over roll station before UV curing. For this reason an excipient which was homogeneous with the polymer was chosen. The propylene glycol and polyethylene glycol (PEG) 300 were replaced by a high molecular

weight glycol (Poloxamer 182), a block copolymer, which formed a nonflocculated homogeneous dispersion, which could be cured by UV radiation. All the dressings had a nominal thickness of 12 mils and were sterilized by EtO.

B. In Vitro Release Kinetics of Silver Sulfadiazine ADDs

The release kinetics for silver sulfadiazine and the water soluble drugs were tested in vitro using established methods employing Franz diffusion cells and water as the dissolution media (11). Quantitative analysis of silver sulfadiazine was performed by HPLC using a UV detector. Chromatography was performed on an Octadecyl Silane (ODS) column using 1% acetic acid-methanol (60:40) as the mobile phase. Silver sulfadiazine was detected at 254 nm. This quantitation was based on the detection of sulfadiazine moiety of the silver sulfadiazine (12).

The elution kinetics for four formulations are reported. Figures 13 and 14 show the release profile of the ADD's containing silver sulfadiazine and chlorhexidine gluconate - Batch No. 003281. Figure 15 shows the release profiles of both clindamycin phosphate and chlorhexidine gluconate - Batch No. 007121. Lastly, figures 16 and 17 are the elution curves for chlorhexidine gluconate from the triple loaded ADD's Batch Nos. 007132 and 009101.

The in vitro analyses of dressings containing any combinations

of clindamycin phosphate and silver sulfadiazine were not carried out for two reasons: (1) the in vivo trials showed that the dressings containing these combinations were no more advantageous than any of the other combinations; and (2) the existing chromatographic methods were not specific enough to distinguish the amount of clindamycin phosphate in the presence of silver sulfadiazine and vice versa. Consequently, no in vitro results of either drug are provided for these formulations (Batch Nos. 007131, 007132 and 009101). However, the release of chlorhexidine gluconate from the triple loaded dressings (Batch Nos. 007132 and 009101) are reported.

The in vitro results for the formulations incorporating silver sulfadiazine indicate that the maximum amount of drug eluted from the dressing was less than 1% of it's loading. Nevertheless, the in vivo results demonstrated this loading to be effective.

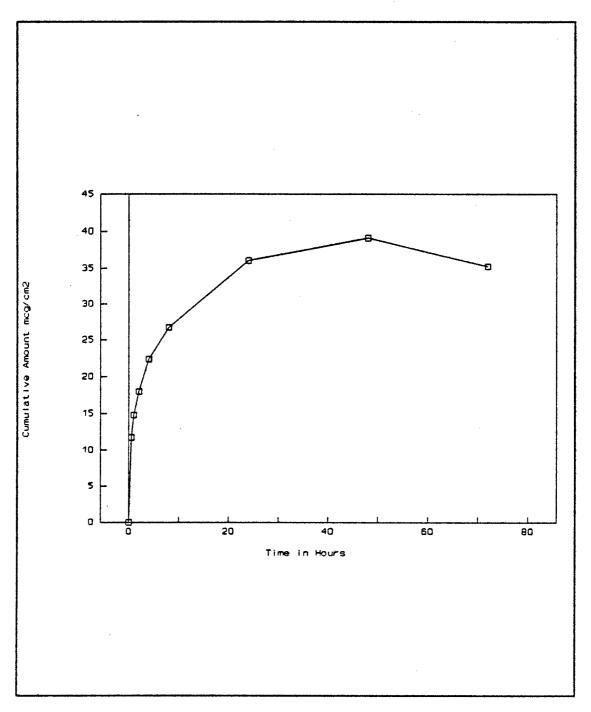


Figure 13. Release Profile of Silver Sulfadiazine from a Dual Loaded ADD containing 20% Silver Sulfadiazine and 10% Chlorhexidine Gluconate - 12 Mils (B.N. 003281)

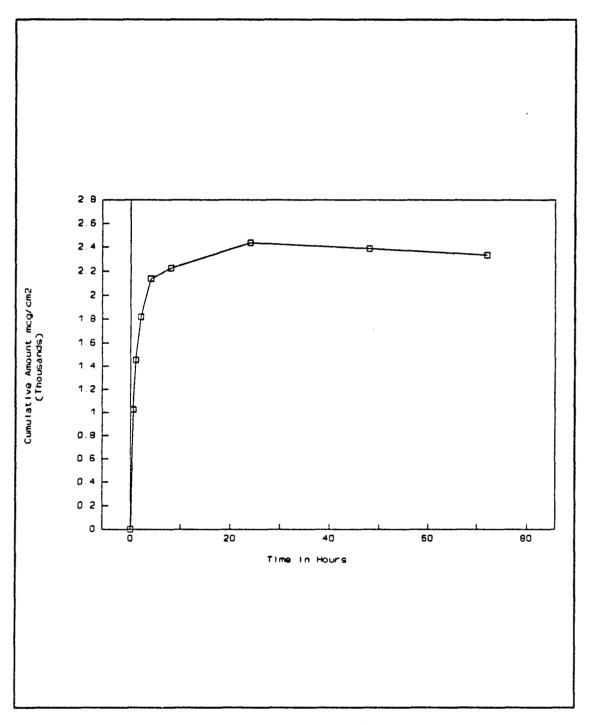


Figure 14. Release Profile of Chlorhexidine Gluconate from a Dual Loaded ADD containing 20% Silver Sulfadiazine and 10% Chlorhexidine Gluconate - 12 Mils (B.N. 003281).

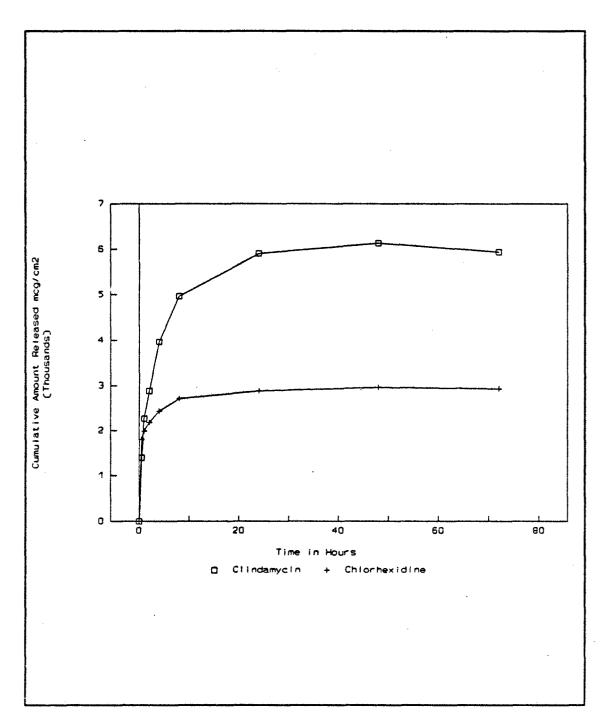


Figure 15. Release Profile of Dual Loaded ADD containing 20% Clindamycin Phosphate and 10% Chlorhexidine Gluconate - 12 Mils (B.N. 007121).

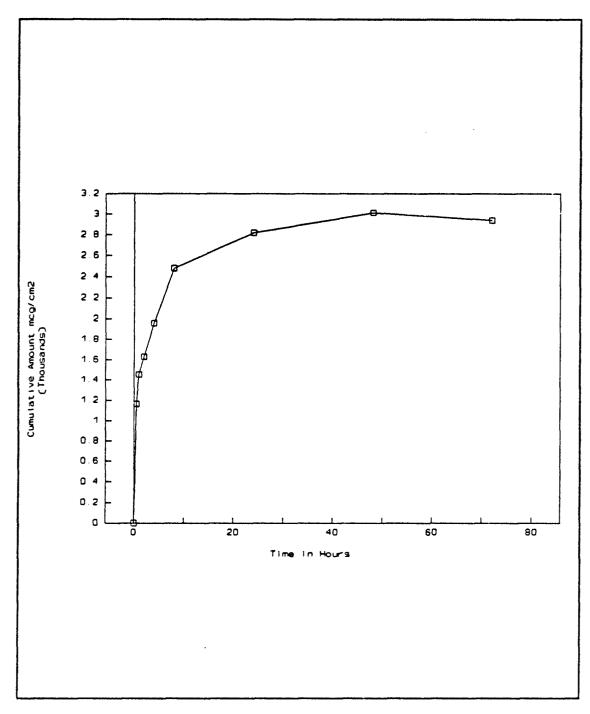


Figure 16. Release Profile of Chlorhexidine Gluconate from a Triple Loaded ADD containing 10% Silver Sulfadiazine, 10% Chlorhexidine Gluconate and 10% Clindamycin Phosphate - 12 Mils (B.N. 007132).

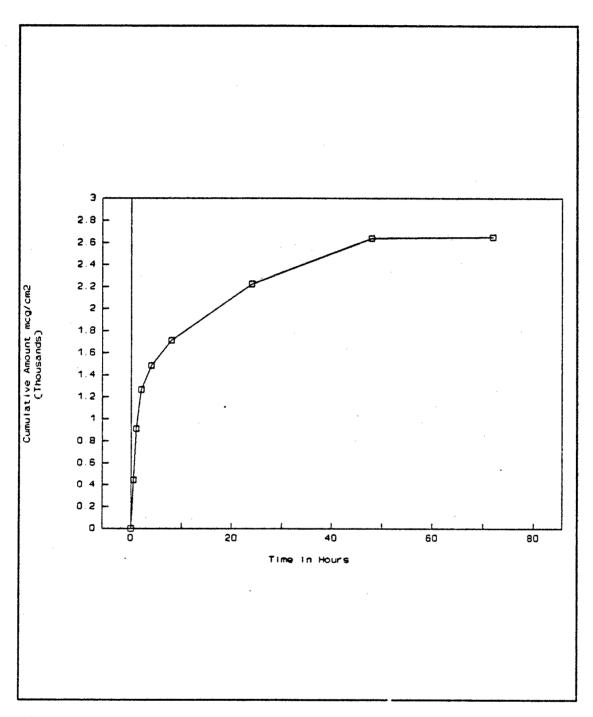


Figure 17. Release Profile of chlorhexidine Gluconate from a Triple Loaded ADD containing 12% Silver Sulfadiazine, 10% Chlorhexidine Gluconate and 12% Clindamycin Phosphate - 12 Mils (B.N. 009101). C. Summary of USAIDR In Vivo Results

The in vivo tests of the ADD's submitted under Task VIII were conducted at the laboratory facilities of USAIDR in Maryland. Five different formulations were tested on inoculated guinea pigs and the results summarized in Table VII.

USAIDR Gp #	N	Staph. aureus Clin. Infection	N	P. aeruginosa Clin. Infection
Formulation 1	5	0	6	0
Formulation 2	6	0	5	1
Formulation 3	5	2	6	4
Formulation 4	5	0	6	1
Formulation 5	-	-	5	3

Table VII. Summary of USAIDR In Vivo Tests - Biopsy Results.

Formulation 1 = 20% Silver sulfadiazine & 10% Chlorhexidine gluconate Formulation 2 = 20% Clindamycin phosphate & 10% Chlorhexidine gluconate Formulation 3 = 20% Silver sulfadiazine & 10% Clindamycin phosphate Formulation 4 = 10% Silver sulfadiazine, 10% Chlorhexidine gluconate & 10% Clindamycin phosphate Formulation 5 = 12% Silver sulfadiazine, 10% Chlorhexidine gluconate & 12% Clindamycin phosphate.

Results of prophylactic tests on animals showed that the formulation containing 20% silver sulfadiazine and 10% chlorhexidine gluconate successfully inhibited clinical infections caused by <u>Staphylococcus aureus</u> and <u>Pseudomonas aeruginosa</u>. These encouraging results led to the recommendation that this formulation was the optimal choice for accelerated stability testing under Task X. TASKS IX AND X

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Tasks IX & X required the preparation, mackaging and sterilization of 500 individual ADD's containing 20 parts silver sulfadiazine and 10 parts chlorhexidine gluconate. All the dressings were die cut from sheet stock which was prepared from a one kilogram batch. This batch was mixed in a stainless steel container with a high shear Hockmeyer mixer for uniform drug dispersion. The sheet stock was prepared immediately after proper dispersion and all the ADD's for Tasks IX & X were fabricated from this sheet stock the following day.

Task IX required the preparation 200 sterile ADD's. Each dressing was individually sealed in an aluminum pouch, labelled and sterilized by electron beam irradiation. These were delivered to USAIDR along with 100 sterile placebos. The remaining ADD's were subjected to a battery of guality control tests. The elution kinetics were also determined and recorded for reference as the initial starting value for the storage stability study. Sample dressings were successfully tested for microbiological zone of inhibition and sterility. Results have been included in the appendix.

A. In Vitro Analysis of Silver Sulfadiazine ADD's

The procedures used for the analysis of these ADD's had to be modified because silver sulfadiazine '. nearly insoluble in water. Distilled water which was previously used as a dissolution media in the receptor cell was not predict . to be effective in extracting silver sulfadiazine from the ADD s. Therefore, the techniques for the HPLC analyses of these ADDs were tested under two conditions: (1) utilizing conventional extraction methods previously employed

to detect the presence of water soluble drugs, and

(2) the extraction of silver sulfadiazine under ideal conditions.

T.e first method (Task VIII-B) was employed to compare the elution rate under the identical conditions previously used for the water soluble drugs, whereas the second method was intended for the specific assay of silver sulfadiazine.

Various solvents were substituted for water to determine an optimal extraction media for the dressing (Table VIII). A thirtyfive percent ammonia solution was chosen as the dissolution medium since silver sulfadiazine is freely soluble in ammonia. The volatility of this media excluded the use of the Franz diffusion cells because of it's open design. As an alternative, a modification of the USP Rotating Bottle method was used for the total extraction of silver sulfadiazine (13). The dressings were placed in tightly capped amber bottles containing the ammonia

solution and extracted for 24 hours in a sieve shaker. The extracts were then diluted and assayed (Appendix III). This procedure allowed the detection of the maximum amount of silver sulfadiazine that could be extracted in vitro from the ADD's.

Solvent	Solubility (mg/100 ml)
Water Dimethyl Sulfoxide 10% w/v Ammonia solution 25% w/v Ammonia solution 35% w/v Ammonia solution Propylene glycol 15% PEG 300 solution 40% PEG solution Oleic Acid Light Mineral Oil	0.11 > 35 > 2.10 ³ > 5.10 ³ freely soluble slightly soluble insoluble slightly soluble slightly soluble

Table VIII. Solubility of Silver Sulfadiazine

Initially, a 1 cm diameter disc of the ADD was placed into a 50 ml amber bottle containing 20 ml of a 25% ammonia solution and extracted for 24 hours using a sieve shaker. Six milliliters of the extract was diluted to 100 ml with distilled water and assayed for silver sulfadiazine. The extraction was performed on three ADD's with a control sample run concurrently. The control sample contained a predetermined amount of silver sulfadiazine. Six milliliters of this solution was diluted to 100 ml like the test samples. The second formulation was also assayed similarly, but to test for content uniformity, thirty 1 cm (diameter) discs, in 3 groups of 10, were extracted. Two sets of controls which bracketed the amounts of silver sulfadiazine contained in 10 discs were also run.

Two formulations of ADD's containing 20% silver sulfadiazine by weight were assayed utilizing this method. The first formulation (B.N. 003281) contained 20% silver sulfadiazine and 10% chlorhexidine gluconate. The second formulation (B.N. 007131) contained 20% of silver sulfadiazine and 10% clindamycin phosphate.

The results of these assays indicate that about 90% of the silver sulfadiazine in the ADD can be extracted under ideal conditions (Table IX). The above procedure was utilized to determine the total silver sulfadiazine content in those dressings undergoing accelerated storage stability. However, these extraction conditions are not representative of those in vivo. Elution of the drug into the wound is hypothesized to be less than that observed under these conditions, because of the high water content associated with the wound.

EXPERIMENTAL mg/Disc AgSdz	THEORETICAL mg/Disc AgSdz	RELEASE % AgSdz
1 Disc/extra	action	
5.03	4.68	107
4.18	4.68	89.3
4.30	4.78	90.0
4.17	4.92	84.7
	mg/Disc AgSdz 1 Disc/extra 5.03 4.18 4.30	AgSdz AgSdz 1 Disc/extraction 5.03 4.68 4.18 4.68 4.30 4.78

Table IX. Results of Silver Sulfadiazine Assay.

- -

10 Discs/extraction

Controls	mg/1 Ag:	ş AgSdz	
Set 1 Set 2	43.3 109.4	46.8 122.1	92.5 89.5
Sample II # A # B # C	50.7 51.1 55.4	57.2 54.2 56.8	88.6 93.2 97.5

AgSdz = Silver sulfadiazine

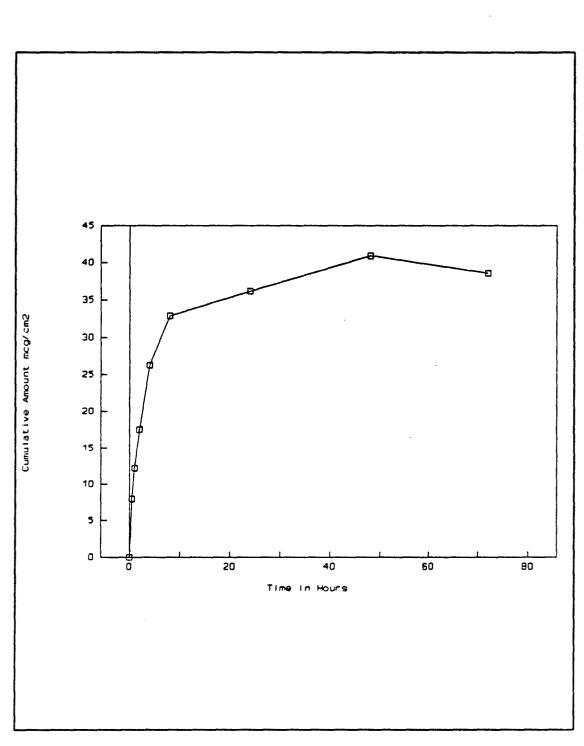
Sample I = 20% Silver sulfadiazine:10% Clindamycin phosphate
 (Batch Nc. 007131)
Sample II = 20% Silver sulfadiazine:10% Chlorhexidine
gluconate
 (Batch No. 003281)

B. Shelf Stability Studies

The ADD's (B.N. 010181 - PDDS2) were tested at five different temperatures for the accelerated shelf stability studies. A group of forty-eight ADD's was placed under each of the five conditions specified below:

- (1) 45⁰ C, 90% R.H,
- (2) 38⁰ C, 90% R.H,
- (3) Room Temperature
- (4) 23^0 C, under water,
- $(5) -40^0$ C.

The elution kinetics of these ADD's were recorded and used as the initial time point (t = 0). These are reported as elution curves, figures 18 and 19.



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Figure 18. Release Profile of Silver Sulfadiazine from a Dual Loaded ADD containing 20% Silver Sulfadiazine and 10% Chlorhexidine Gluconate - 12 Mils (B.N. 010181 - PDDS2).

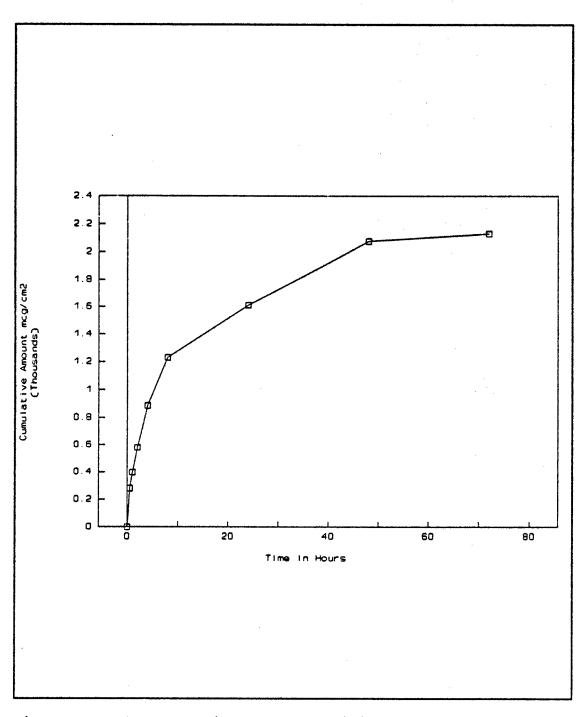


Figure 19. Release Profile of Chlorhexidine Gluconate from a Dual Loaded ADD containing 20% Silver Sulfadiazine and 10% Chlorhexidine Gluconate - 12 Mils (B.N. 010181 - PDDS2).

CONCLUSIONS

Thermedics Inc. has developed two sustained release Antimicrobial Dermal Dressings. Both types of dressings incorporate antimicrobial agents to prevent infection in superficial lesions for periods up to 72 hours.

The first formulation, a chlorhexidine gluconate ADD, was formulated and tested successfully on guinea pigs. This dressing was effective in vivo against <u>Strep. pyogenes</u>, <u>Staph. aureus</u> and <u>P. aeruginosa</u> under prophylactic conditions. A six month accelerated stability task is entering its fourth month of testing. Analysis of the results up to the two month period show no instability in the product under accelerated conditions.

The second formulation, a chlorhexidine gluconate - silver sulfadiazine ADD, was also fabricated and tested on guinea pigs. This too showed promising results against <u>Staph. aureus</u> and <u>P.</u> <u>aeruginosa</u> under prophylactic conditions. The effectiveness of this dressing against <u>Candida</u> remains to be evaluated.

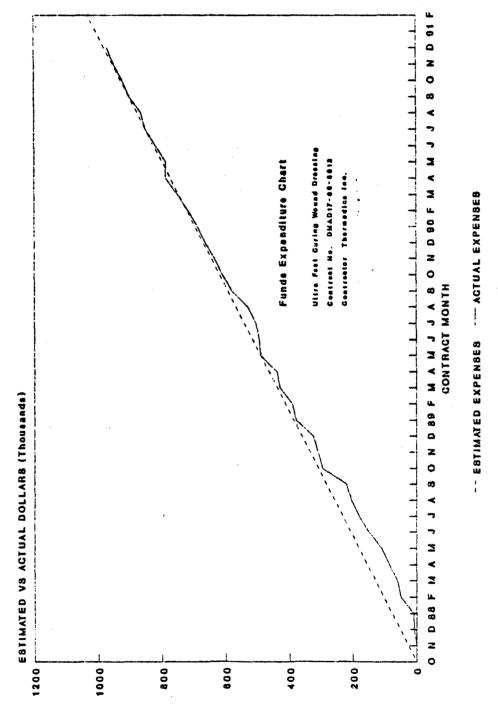
In conclusion, all tasks have been completed or are in progress. Resulting dressings have been shown to meet the design requirements of being easy to apply and effective against selected organisms.

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13. Physical Tests and Determinations, <u>USP/NF_XXII</u>, 1578, (1990).



Attachment to Data Item A-5001B

APPENDIX I

CERTIFICATE OF ANALYSIS

REPRODUCED FROM FERMION CERTIFICATE OF COMPLIANCE

J.

Product				
CHLORHEXIDINE	GLUCONATE			
Batch No. 895580	Quantity 20kg			
Date of manufacture:	May 1989	BP Requirements		
Indentification	Positive (IR)	Positive (test A=IR)		
Colour	Almost Colourless	Almost Colourless to pale straw-coloured		
Odour	Odourless	Odourless or almost Odourless		
Sulphated Ash	0.01%	< 0.1%		
PH	6.6	5.5 - 7.0		
Assay	20.4 %w/v	19.0 -21.0% w/v		
p-Chloroaniline	< 10 ppm	< 500ppm		
Related Substances (HPLC)	1.2%	< 3%		
Density	1.06 g/ml	1.06 - 1.07 g/ml		
THE MATERIAL COR	RESPONDS TO THE REQU	IREMENTS OF BP		
Date of analysis Date of expiry				
Signature Espoo, S	eptember 1st, 1989			
Orion Co fermion	Orion Corporation fermion			
Signature on File Tuula Hauta-aho M.SC Quality Control Chemist				

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002031-FDD5-1



E-BEAM SERVICES, INC.

CERTIFICATE OF IRRADIATION

CUSTOMER: THERMEDICS CUSTOMER ORDER: 33990 PRODUCT: SURGICAL DRESSINGS PROCESSING CENTER: CRANBURY, NEW JERSEY SIDES IRRADIATED: ONE DATE IRRADIATED: AUGUST 15, 1990 EBS JOB NUMBER: E15286-3 EBS LOT NUMBER: 901508

PRODUCT CODE	LOT #	NUMBER AVE OF UNITS	E SURFACE DOSE IN MRADS
SURGICAL DRESS	NGS	1	2.4

Certified by: Nexuse Cascarett Approved by:

E-BEAM SERVICES, MO

DES #9000715 DISK #3-90

Thermedics Inc.

CERTIFICATE OF ANALYSIS

Antimicrobial Dermal Dressings

Dat	e				:	September	4, 1990.
30%	Chlorhexidine	Glud	conate	ADD's	:	Batch # 00	8031 PDDS1
Des	cription	:	matrix adhes:	x; rein ive ba se lind	nforced cking,	5 inch drug 1 by a 2.5 x 2 covered by a packaged in a	2.5 inch removable
Col	or	:	White	to Of:	f-white		
	ckness total perimeter				0.014 m 0.013 m		
Wei	ght total		1.440	g ± 0	.019 g.		
Ide	ntification (I.R.)	:	compl	ies.			
Dis	solution time	:	> 2.5	mg.p	er cm².	in 24 hours	
Bio	logical Activit P. aeruginosa S. aureus	a		tive.	990		
	rility (USP XXII, 1990		passe:	S			
Ass	ау	:	135 m	g. chl	orhexid	ine gluconat	e/ADD.

Chemist

9/7/30

470 Wildwood Street • P.O. Box 2999 • Woburn, MA 01888-1799 • (617) 938-3786 • Telex 7557644 • FAX (617) 933-4476

	15 HAWKINS AVENUE, EPPING 1, CAPE TOWN TELETEX (0) 53-84 P.O. BOX 253, EPPINDUST 74-5 SOUTH AFRICA FAX NATIONAL: (0) TELEPHONE: (021) 531-8421 FAX INTERNATION	
ANALYTICAL N.	0 1610	BATCH Nº SRP 4
DATE	7/89	CODE 6002
PRODUCTI BILVE	R BULFHADIAZING (MICRONEARD) BPECIFICATION	RESULT
DESCRIPTION	MILTE OR ALMOST WILLE POWDER	Complie
IDENTIFICATION	I.R. CONCORDANT WITH REFERENCE STD.	Complie
	MAX. 1,0N	0,10%
LOSS ON DRYING		
LOSS ON DRYING	млх. 300 ррм	COMPLIE
	MAX. 300 PPM 27,28 TO 32,08	27,8%
NITRATE	27,28 TO 32,08	

APPROVED:

Mee

QUALITY ASSURANCE MANAGER

Refer Inquiries To: Ceres Chemical Co. Inc. 5 Teramar Way White Plains, NY, USA 10605 Phone: 914 - 949-5337 Fax: __914 - 997-7042

سماد محمد



E-BEAM SERVICES, INC. 32 Melrich Road Cranbury, New Jersey 08512

CERTIFICATE OF IRRADIATION

CUSTOMER: THERMEDICS INC. CUSTOMER ORDER: 2466 PRODUCT: WOUND DRESSING SAMPLES PROCESSING CENTER: CRANBURY, NEW JERSEY SIDES IRRADIATED: ONE DATE IRRADIATED: OCTOBER 30, 1990 EBS JOB NUMBER: E15698-3 EBS LOT NUMBER: 903010

PRODUCT	LOT •	NUMBER OF UNITS	AVG. SURFACE DOSE
WOUNG DRESSING	2.5 rr	1 CASE	2.5

har Certified by: . Approved by:

E-BEAM SERVICES, INC.

QE5 \$9001003 DISK \$4-90

APPENDIX II

MICROBIOLOGICAL TEST RESULTS



225 Wildwood Ave., Woburn, MA 01801 Telephone: (617) 933-6903 Fax: (617) 933-9196

TEST RESULT CERTIFICATE

Client: Thermedics, Inc.

Address: 470 Wildwood Avenue P.O. Box 2999 Woburn, MA 01888-1799 Date of Test: 08/28/90 Test Completion: 09/04/90

P.O. #: 24156-897

Project #: 90-1835

Contact: R. Thirucote

TEST ARTICLE DESCRIPTION: Chlorhexidine Gluconate Dressing

Lot# N/A

NAME OF STUDY: Membrane Filtration Sterility

REFERENCE: USP XXII, 1990, Pp. 1483-1488.

GENERAL PROCEDURE: The test articles (2 units) were aseptically pooled with 300 ml of Fluid D. The extract was then decanted into a sterile container and filtered though a sterile membrane filter. The membrane was then removed from the filter holder and cut in half. One half was immersed in 100 ml of Fluid Thioglycollate Medium (FTM) and one half was immersed in 100 ml of Trypticase Soy Broth (TSB). Each vessel was incubated at 30-35°C and 20-25°C respectively. The contents of each vessel were examined for growth during the 7 day incubation period.

RESULTS: There was no growth observed in either media inoculated with the test article during the 7 day observation period.

CONCLUSION: The test article is considered sterile according to the procedures outlined in USP XXII via membrane filtration technique.

AUTHORIZED PERSONNEL:

Steven P. Lynn, Ph.D Study Director

Susan Yadlon,

Quality Assurance

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Specialists in Toxicology

TEST ARTICLE DESCRIPTION: Chlorhexidine Gluconate Dressing

LOT #: N/A

NAME OF STUDY: Zone of Inhibition

REFERENCE: Based on the method described in USP XXII, 1990.

GENERAL PROCEDURE: The test article was analyzed for its ability to produce a zone of inhibition against cultures of Staphylococcus aureus (S. aureus) and Pseudomonas aeruginosa (P. aeruginosa). The test article (three 0.8 cm diameter discs) and placebo discs (three 0.8 cm diameter discs) were placed on the surface of Trypticase Soy Agar containing the test organism. The positive control for S. aureus was a mixture of penicillin and streptomycin. The positive control for P. aeruginosa was ampicillin. The negative control for both organisms was an untreated filter disc. Three plates were used for each determination. The plates were inverted and incubated at $30-35^{\circ}$ C for 72 hours.

RESULTS:

			Zoi	ne of	Inhibition	(in	Cm)	
		S. at	ireus			₽.	aerugin	osa
<u></u>	1	2	3	Ave	1	2	3	Ave
Neg. Control	0	0	0	0	0	0	0	0
Pos. Control	1.40	1.30	1.30	1.33	2.	0 2	.0 2.0	2.0
Test Article	1.50	1.80	1.70	1.67	1.5	0 1	.60 1.50	1.53

TEST ARTICLE DESCRIPTION: Combination Silver Sulfadiazine/ Chlorhexidine Gluconate Dressing

LOT #: B.N. 010181-PDDS2

NAME OF STUDY: Zone of Inhibition

REFERENCE: Based on the method described in USP XXII, 1990.

GENERAL PROCEDURE: The test article was analyzed for its ability to produce a zone of inhibition against cultures of Staphylococcus aureus (S. aureus) and Pseudomonas aeruginosa (P. aeruginosa). The test article (three 0.8 cm diameter discs) and placebo discs (three 0.8 cm diameter discs) were placed on the surface of Trypticase Soy Agar containing the test organism. The positive control for S. aureus was a mixture of penicillin and streptomycin. The positive control for P. aeruginosa was ampicillin. The negative control for both organisms was an untreated filter disc. Three plates were used for each determination. The plates were inverted and incubated at $30-35^{\circ}$ C for 72 hours.

RESULTS:

			Zo	ne of	Inhibiti	on (in cm	1)	
		s. a	ureus			<u>,</u>	P. ae	rugin	osa
	1	2	3	Ave		1	2	3	Ave
Neg. Control	1 0	0	0	0		0	0	0	0
Pos. Control	1 1.2	1.1	1.8	1.37		1.9	1.8	2.0	1.9
Test Article	e 1.6	1.4	1.7	1.57		1.4	1.5	1.6	1.5

TEST ARTICLE DESCRIPTION: Combination Silver Sulfadiazine/ Chlorhexidine Gluconate Dressing

Lot#: 010181-PDDS2

NAME OF STUDY: Membrane Filtration Sterility

REFERENCE: USP XXII, 1990, Pp. 1483-1488.

GENERAL PROCEDURE: The test articles (2 units) were aseptically pooled with 300 ml of Fluid D. The extract was then decanted into a sterile container and filtered though a sterile membrane filter. The membrane was then removed from the filter holder and cut in half. One half was immersed in 100 ml of Fluid Thioglycollate Medium (FTM) and one half was immersed in 100 ml of Trypticase Soy Broth (TSB). Each vessel was incubated at 30-35°C and 20-25°C respectively. The contents of each vessel were examined for growth during the 7 day incubation period.

RESULTS: There was no growth observed in either media inoculated with the test article during the 7 day observation period.

CONCLUSION: The test article is considered sterile according to the procedures outlined in USP XXII via membrane filtration technique.

APPENDIX III

ASSAY METHODOLOGY FOR

IN VITRO RELEASE KINETICS

HPLC Method for the Analysis of Silver Sulfadiazine In Vitro Using Ultraviolet Detection.

Quantitative analysis of silver sulfadiazine was performed by HPLC using a UV detector. The method was linear and precise and can be used for determining sample concentrations as low as one microgram per milliliter. The chromatographic conditions used for the analysis are outlined below.

<u>Materials</u>

Chromatography was performed on an AllTech OctaDecyl Silane (ODS) column (4.6 mm x 250 mm - 5 u) using 1% acetic acid-methanol (60:40) as the mobile phase. The flow rate was adjusted to 1 ml/min using a Waters Solvent Delivery Module (Model 590). One microliter (1 ul) injections of the sample were introduced through a Waters U6K injector and the sample quantified by means of a Waters 441 UV Absorbance Detector, connected to a Shimadzu Integrator (Model CR601 - Chromatopac). Silver sulfadiazine was detected at 254 nanometers.

Method

This quantitation was based on the detection of sulfadiazine moiety of the silver sulfadiazine (12). This method is useful in determining drug solutions with concentrations of 1 mcg/ml and

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above. Example chromatograms for 10 and 25 mcg/ml of silver sulfadiazine are shown in figure A3.1. Silver sulfadiazine standard solutions were prepared and used to generate a standard calibration curve, plotting concentration versus area shown in figure A3.2.

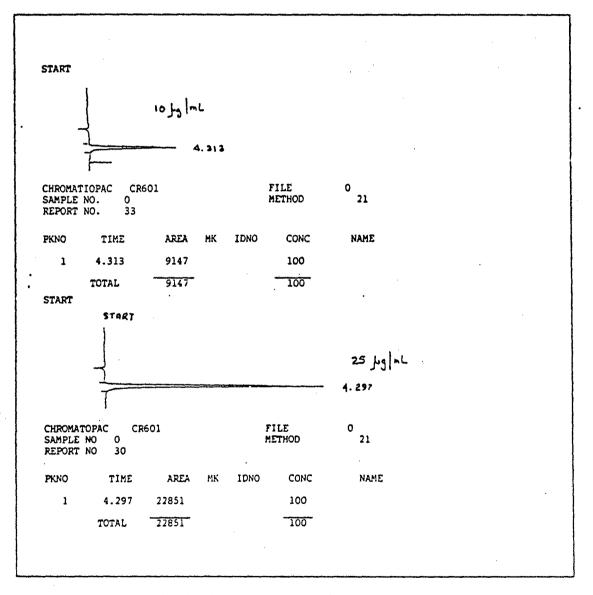


Figure A3.1. Typical Chromatograms for Silver Sulfadiazine

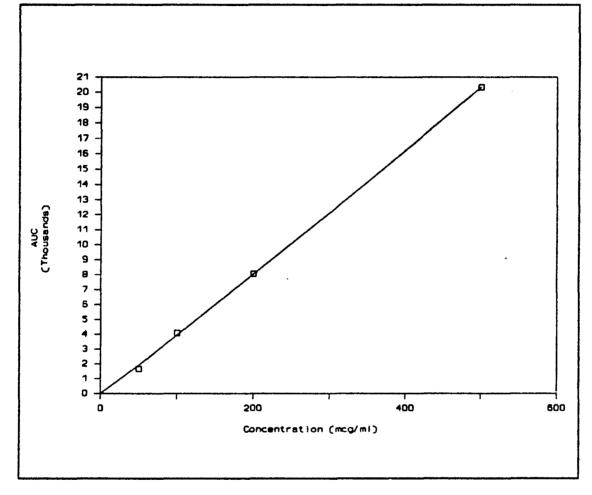


Figure A3.2 Typical Calibration Curve Obtained for Silver Sulfadiazine Assay

APPENDIX IV

IN VITRO DATA SHEETS

TITLE : Formulation 1 - Chlorhenidine gluconate - 30% Envipient 30%

	238 nm	TION CU	RVE					lverage Val dil adj	125	
ncg/nl	YOC	YOC	AVGAUC		Er.			ncg/ni	ncg/cn2	वेंसे प/टच्ची
		_								
0		-			0.0		0.0		0.0	0.0
	419997				1		146.6			454.4
	953607				4		263.7		828.7	374.3
	1466489				8		243.4			-51.7
	1982141				24		330.6			268.7
	2264835				%		314.7			-42.5
	2895387				72		334.4	312.2	%8.0	-33.3
	3207704	379/073								
	3747448 4008633	2006-204	3747448 2007464							
<u>-</u>										
	Regressio	a Output:								
onstant			160605							
	ź I Est		161794.8							
Square			0.987588							
	servation: f Preedo		10 8							
Creffic	ient(s)	3988.658								
td Err o	t Coef.	157.4464								
ER.	Å æ	a	8 cel		Çc	el	¥4(). STD.		
;	Q	0	0	0	0	0	0	0		
	818991	798989	-	02816	-	-	745236.3	-		
	1231903		1210578		1194239			15421.11		
8	1105076		1220024		1069403			54267.06		
	1620899		1307438		1509503			129742.1		
	1731935		1191389		1324270			229985		
72	1569225		1199845		1354928		1374666	151443.7		
araulati		肥子						01/04/90		
hlorhens		30					<u>P1e</u>	CEG3030.XI	G	
ropylese	e gi y cal	30 40								
ligoner										

60

HER / 33/044 - FAX (01/) 933-44/6

ELUTION RATE WORKSHEET FOR CHLOREEXIDINE GLUCONATE "A"

TITLE : Formulation 2 - Chlorbenidine glucomate 30% PG 5% PEG 24% (6 Mil Thick)

STANDAR	D CALIERI	ATION CU	RVE									
2	238 nu				Data of Average Values dil adj							
ncg/nl	AUC	ACC	AVGAUC	Er.	ncg/nl	ncg/ni	ncg/cm2	dif u/cml				
0	0	0	0	0.0	0.0	0.0	0.0	0.0				
100	651553	635565	643559	0.5	382.4	382.4	1092.1	1082.1				
500	2514236	2497240	2505738	1	469.1	478.7	1354.7	272.6				
1000	5739827	5778169	5758998	2	542.2	553.9	1567.6	212.9				
2000	11708183	11925306	11816745	4	658.9	572.5	1903.2	335.6				
				8	906.5	923.1	2612.4	709.2				
				24	1196.8	1219.4	3451.0	838.6				
				48	1398.0	1427.9	4040.9	589.9				
				72	1340.5	1375.5	3892.6	-148.3				

Regression Output:

Constant	-115536
Std Err of Y Est	235621.5
R Squared	0.99822
No. of Chservations	5
Degrees of Freedom	3

X Coefficient(s) 5917.423 Std Err of Coef. 144.2521

ER.	h œl		5 celi		C celi		AVC	.	STD.
G	0	٥	0	٥	đ	0	0		0
0.5	1973020	2	799643		1668525		2147063	477894	1.8
1	2620418	2	370018		2490857		2650431	157356	4
2	3299509	3	154345		2524517		3092790	406771	.4
4	4385335	3	85082		2980627		3783681	590887	9
8	5521057	6	586390		3640809		5249419	121777	2
24	6885551	3	171294		5941804		6966216	871229	.8
48	7539842	10	111254		6519321		8156806	164767	9
72	7648551	8	775144		7026920		7816872	723565	.6
Pornulati	10	HL.				!	Date:	01/04/9	¥)
Chlorheri	line	30					File	PORM2	
Propylene	glycol	. 6				,			
PEG 300		24							
Oligoner		40							

ELUTION RATE WORKSHEET FOR CHLORESTIDINE GLUCONATE "A"

TITLE : Formulation 3 - Chlorberidine gluconate 30% PG 6% PEG 24% (20 Mil Thick)

STANDAR	D CALIER	ATION CO	IRVE									
:	238 nm				Data of Average Values							
					d	il adj						
ncg/nl	AUC	AUC	AVGAUC	Er.	ncg/ni	ncg/nl	ncg/cm2	∰ u/cm2				
0	0	0	0	0.0	0.0	0.0	0.0	0.0				
100	651553	635565	543559	0.5	298.2	298.2	843.8	843.8				
500	2514236	2497240	2505738	1	409.0	416.4	1178.5	334.7				
1000	5739827	5778169	5758998	2	561.7	571.9	1613.6	440.0				
2000	11708183	11925306	11916745	4	993.8	1007.9	2852.3	1233.8				
				8	1574.6	1599.4	4526.4	1674.0				
				24	2549.3	2588.7	7325.9	2799.5				
				48	2725.9	2789.6	7894.6	568.7				
				72	2557.5	2625.5	7430.5	-464.1				

Regression Of	it put:
Constant	-115536
Std firr of I Est	235621.5
R Squared	0.99822
No. of Observations	5
Degrees of Freedom	3

I Coefficient(s) 5917.423 Std Err of Coef. 144.2521

E .	A cell		8 œ‼		C व्या		AVC	;. s	173.
0	0	Q	9	0	0	0	0	(}
0.5	1577230	1	770000	1	599073		1648768	86136.7	7
1	2133259	24	95282	z	295272		2304604	148426.	1
2	2678531	- 43	.44504	28	01945		3208327	663891.	3
- 4	5226736	76	41917	4	27834		5765462	1365282	2
8	9556287	11	81585	67	16774)		9201504	1859770	1
- 24	14175602	178	175577	128	158062	1	1959747	2123969	}
48	16012158	17,	23839	14	47317	ŀ	5014505	1280277	1
72	15717976	144	44287	148	92344	1	5018169	527499	I
Formulati	01	WE				و	ate:	01/04/9	0
Chlorheris	dine	30				?	<u>]</u> e	CHT305	24.881
Cropylene	giyool	6							
PEG 300		24							
Oligoner		40							-

ELUTION RATE WORKSHEET POR CHLORHEXIDINE GLUCONATE "A"

4

TTT. # •	Tormulation	4 Chlorhenidine	Guernate	30:5:24	(16 16)	Thick)
		- Currennie	WILLIALE	30-0-49	110 1212	

:	238 nm				Data of Average Values dil adj						
ncg/nl	AUC	AUC	AVGAUC	Hr.	acg/ai	ncg/nl	ncg/cn2	dif u/ca2			
0	0	0	0	0.0	0.0	0.0	0.0	0.0			
100	703326	682639	692983	0.5	935.8	935.8	2648.4	2548.4			
500	2954195	3074364	3014280	1	1274.3	1297.7	3672.5	1024.1			
906	5010641	4889083	4949862	2	1655.4	1687.3	4775.0	1102.5			
1000	6573677	6496506	6535092	4	1969.5	2010.9	5690.8	915.8			
2000	12303308	12315480	12309644	8	2355.7	2405.0	6806.1	1115.4			
				24	2569.0	2627.9	7437.0	630.9			
				48	2718.0	2782.2	7873.6	436.6			
				72	2597.8	2665.8	7544.1	-329.5			

7691 200 1	m ombar	•
Constant		51238.14
Std Err of Y Est	176077.4	
R Squared	0.998787	
No. of Observation	5	6
Degrees of Preedo	4	
I Coefficient(s)	6180.552	
Stá Err of Coef.	107.5904	

in Autout

ER.	λa		Bo		C	œl	VV	J. S	TD.
0	0	0	0	0	0	0	0	(}
0.5	6162364	5844701	5047972	5148581	6396019	6411232	5835145	554471	4
1	8502389	8017478	7277155	7176790	8090149	8498521	7927080	528776.	3
2	10917151	10434510	9804288	9301672	10876334	10361538	10282582	573800.	9
4	13028399	12147710	10957414	10951975	13246477	13010390	12223728	960818.	5
8	15075334	14767530	13264084	12681579	15488668	15389080	14611063	1285044	ł
24	17731750	17421828	14579678	13964830	16488668	15389080	15929306	1400108	}
48	17807891	18194299	14970653		16426199		16849761	1268488)
72	17278600		13927516		17115546		16107221	1542721	•
Formulati	01	WL1					Date:	1/31/90	
Chlorheri	dine	ŰČ					Pile	PORH4	
Propyien	Glycai	6							
PEG 300		24							
Oligoner		40							

ELUTION RATE WORKSHEET FOR CHLOREEXIDINE GLUCONATE "A"

TITLE : Formulation 15 Chlorhenidine glucomate 30:6:24 (12 Kil Thick)

	D CALIERI	ATION CU	RVE							
	238 nm							lverage Val dil adi	ues	
ncg/nl	AUC	AUC	AVGAU	C	Er.		ncg/ni		ncg/cn2	dif u/cm2
0	G	0	0		0.0		0.0	0.0	0.0	0.0
100		582007			0.5		657.6		1860.3	1860.3
500	2904176	2735056	2819616		1		818.4	834.8	23£2.5	502.2
	5015976				2		975.8		2819.5	457.0
	5758511	5959114			- 4		1260.2		3635.5	816.0
2000	12353230		12353230		8		1381.0	-		362.0
					24		1558.1		4507.2	509.8
					48		1612.6			166.8
					72		1590.5	1630.8	4615.2	-58.8
Constant Etd Err o R Square	rf I Lst	·	- <u>109338</u> 162676.9 0.9989 6 4 6							
)egrees (Coeffici	of Preedo ient(s) of Coef. A ce	5178.834 99.49458	4	<u></u>	C c		A V(1. STD.	*******	
Degrees (Coeffici Std Err (ient(s) of Coef.	5178.834 99.49458	4	<u></u> 0		 zeli		. std.		
Degrees of Coeffici Std Err of HR. 0	ient(s) of Coef. A ce 0	n 6178.834 99.49458 	4 B a	0	0	0	0	Q	********	
Degrees (Coeffici Std Err (ER. 0 0.5	ient(s) of Coef. A ce 0 4383009	5178.834 99.49458 <u>лі</u> 0 43355936	4 B a 0	0 3223369	0 4355315	0 4154770	0 3952399	Q		
Degrees (Coeffici Std Err (ER. 0 0.5 1	ient(s) of Coef. A ce 0 4383009	178.834 99.49458 11 0 4335936 5539882	4 9 a 0 3261997 4124541	0 3223369 3925514	0 4355315 5083896	0 4154770 5191840	0 3952399	0 507273.9 597227		
Degrees (Coeffici Std Err (HR. 0 0.5 1 2 4	ient(s) af Coef. A co 4383009 582(618 6440575 8779358	178.834 99.49458 <u>11</u> 0 4335936 5539882 6636586	4 B a 0 3261997 4124541 5196536 7270268	0 3223369 3925514 5119882	0 4355315 5083896 6113629 7212876	0 4154770 5191940 5008724	0 3952399 4947232 5920155 7677336	0 507273.9 597227 576687.1 702542.3		
Degrees (Coeffici Std Err (ER. 0 0.5 1 2 4 8	ient(s) af Coef. A ce 4383009 5826618 6440575 8779358 9323445	178.834 99.49458 <u>11</u> 0 4335936 5539882 6636586	4 B a 0 3261997 4124541 5196536	0 3223369 3925514 5119882	0 4355315 5083896 6113629	0 4154770 5191940 5008724	0 3952399 4947232 5920155 7677336	0 507273.9 597227 576687.1		
Egrees of Coefficients Coeffici	ient(s) af Coef. A co 4383009 5826618 6440575 8779358 9323445 11124611	n 5178.834 99.49458 <u>11</u> 0 4335936 5539882 6636586 8546321	4 9 a 0 3261997 4124541 5196536 7270268 8633315 10153656	0 3223369 3925514 5119882	0 4355315 5083896 6119629 7212876 7314363 7276191	0 4154770 5191940 5008724	0 3952399 4947232 5920155 7677336 8423708 9518153	0 507273.9 597227 576687.1 702542.9 833488.3 1634112		
ER. 0 0.5 1 2 4 8 24 43	ient(s) af Coef. A co 4383009 5826618 6440575 8779358 9323445 11124611 11366454	178.834 99.49458 11 0 4335936 5539882 6636586 8546321	4 9 a 0 3261997 4124541 5196536 7270268 8633315 10153656 10437533	0 3223369 3925514 5119882	0 4355315 5083896 6113629 7212876 7314363 7276191 7760853	0 4154770 5191940 5008724	0 3952399 4947232 5920155 7677336 8423708 9518153 9854947	0 507273.9 597227 576687.1 702542.9 833488.3 1634112 1528538		
ER. 0 0.5 1 2 4 8 24 43	ient(s) af Coef. A co 4383009 5826618 6440575 8779358 9323445 11124611	178.834 99.49458 11 0 4335936 5539882 6636586 8546321	4 9 a 0 3261997 4124541 5196536 7270268 8633315 10153656	0 3223369 3925514 5119882	0 4355315 5083896 6119629 7212876 7314363 7276191	0 4154770 5191940 5008724	0 3952399 4947232 5920155 7677336 8423708 9518153 9854947	0 507273.9 597227 576687.1 702542.9 833488.3 1634112		
Legrees of Coeffici Std Err of ER. 0 0.5 1 2 4 8 24 4 8 24 4 8 72	ient(s) af Coef. A ce 0 4383009 5826618 6440575 8779358 9323445 11124611 11366454 11390722	n 5178.834 99.49458 11 0 4335936 5539882 6636586 8546321	4 9 a 0 3261997 4124541 5196536 7270268 8633315 10153656 10437533	0 3223369 3925514 5119882	0 4355315 5083896 6113629 7212876 7314363 7276191 7760853	0 4154770 5191940 6008724 7073021	0 3952399 4947232 5920155 7677336 8423708 9518153 9854947 9718106	0 507273.9 597227 576687.1 702542.9 833488.3 1654112 1528538 1659348		
Coeffici Std Err of ER. 0 0.5 1 2 4 8 24 4 8 24 4 8 72 70rmulati	ient(s) af Coef. A co 4383009 5826618 6440575 8779358 9323445 11124611 11366454 11390722 cm	n \$178.834 99.49458 11 0 4335936 \$5539882 \$636586 8546321 %L\$	4 9 a 3261997 4124541 5196536 7270268 8633315 10153656 10437533 10307253	0 3223369 3925614 5119882 7192172	0 4355315 5083896 6113629 7212876 7314363 7276191 7760853	0 4154770 5191940 6008724 7073021	0 3952399 4947222 5920155 7577336 8423708 9518153 9854947 9718106 Date:	0 507273.9 597227 576687.1 702542.9 833488.3 1634112 1528538 1659348 02/13/90		
Coeffici Std Err o ER. 0 0.5 1 2 4 8 24 4 8 24 4 8 72 24 5 72 24 24	ient(s) af Coef. A co 4383009 5826618 6440575 8779358 9323445 11124611 11366454 11390722 cm dine	n 5178.834 99.49458 11 0 4335936 5539882 6636586 8546321 %L.% 30	4 9 a 0 3261997 4124541 5196536 7270268 8633315 10153656 10437533	0 3223369 3925614 5119882 7192172	0 4355315 5083896 6113629 7212876 7314363 7276191 7760853	0 4154770 5191940 6008724 7073021	0 3952399 4947232 5920155 7677336 8423708 9518153 9854947 9718106	0 507273.9 597227 576687.1 702542.9 833488.3 1654112 1528538 1659348		
Coeffici Std Err of ER. 0 0.5 1 2 4 8 24 4 8 24 4 8 72 70rmulati	ient(s) af Coef. A co 4383009 5826618 6440575 8779358 9323445 11124611 11366454 11390722 cm dine	n \$178.834 99.49458 11 0 4335936 \$5539882 \$636586 8546321 %L\$	4 9 cc 3261997 4124541 5196536 7270268 8633315 10133656 10437533 10307253 "Machine,	0 3223369 3925614 5119882 7192172	0 4355315 5083896 6113629 7212876 7314363 7276191 7760853	0 4154770 5191940 6008724 7073021	0 3952399 4947222 5920155 7577336 8423708 9518153 9854947 9718106 Date:	0 507273.9 597227 576687.1 702542.9 833488.3 1634112 1528538 1659348 02/13/90		

ELUTION RATE WORKSHEET FOR CHLORHEXIDINE GLUCONATE "A"

TITLE : Formulation 11 Chlorheridine Gluconate 30:6:24 (6 Kil Thick) Gamma Sterilized

2	238 an			Data of Average Values dil adj						
ncg/nl	AUC	ACC	AVGAUC	Er.	ncg/ni	ncg/nl	meg/cm2	dif u/cad		
0	Û	Û	0	0.0	0.0	0.0	0.0	0.0		
100	681894	650123	666009	0.5	559.6	559.6	1583.8	1583.8		
500	2995525	3094110	3044818	1	682.3	696.3	1970.6	386.8		
800	4726613	4823270	4774942	2	855.7	872.8	2470.0	499.4		
1000	6020085	6501856	6260971	4	902.6	924.0	2614.9	144.9		
				8	956.2	978.8	2769.9	154.9		
				24	972.1	996.0	2818.7	48.9		
				48	988.1	1012.4	2865.0	46.3		
				72	962.3	987.0	2793.1	-71.9		

Regression Output:

Constant	2931.184
Std Err of Y Est	110653.9
R Squared	0.998698
No. of Observations	5
Degrees of Freedom	3
-	

X Coefficient(s) 6138.368 Std Err of Coef. 127.9428

HR.	à œ	1	8 a	1	¢c	비	AVC	. std.
G	0	0	0	0	0	٥	0	0
0.5	3612056	3559875	2585731	2559203	4197235	4115444	3438257	655637.5
1	4950850		2990349		4632875		4191358	859105.7
2	6474852		3699925		5592414		5255730	1157604
4	6531353		4416323		5682742		5543473	859055
8	6875060		4780450		5961560		5872357	857444.1
24	7746381		4837630		5326343		5970118	1271755
48	6747297		5320714		6136267		6063093	584391.7
72	6804034		5161434		5763556		5909675	678501.6
Formulati	00	HE.					Date:	11/17/89
Chlorheni	dina	30					Pile	Formil
Propylene	Glycol	6						
PEG 300	•	24						
Oligomer		40						

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ELUTION RATE WORKSHEET FOR CHLOREEXIDINE GLUCONATE "A"

TITLE	Chiar	heridine	Gluconate	ADD's	B.N.	008031E-PDDS1	(Set 1)	}
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STANDAR	O CALIBRI	ATION CU	RVZ					
:	238 nm					rerage Val	ues	
					(iil zoj		
ncg/ni	ACC		AVGAUC	Ur.	acg/al	ncy/ni		dif u/cm2
0	0	0	•	0.0	0.0	0.0	0.0	0.0
100				0.5	434.5	434.5	1229.7	1229.7
	2907409		-	1	528.0	538.9	1525.1	295.3
	4823876			2	740.8	751.0	2133.8	608.7
	6348941			4	1143.6	1162.1	3288.9	1155.1
2000	13401626	12688172	13044899	8	1418.7	147.3	4095.9	807.0
				24	1562.4	1597.9	4521.9	425.0
				48	1749.1	1788.1	5060.4	538.5
				7	1652.4	1696.1	4800.0	-260.5
Constant Std Err (af I Est	n ontan	-176096 200957.2					
	eservation of Freedo ient(s)	6537.082 122.9071		C œl		STD		
ia, af Ob Degrees o I Coeffici Rd Err o HR.	servation of Freedo imit(s) of Coef. A ce	n 6537.082 122.9071 	5 4 B cell					
ia. af Ob Degrees : I Coeffici Ed Err (HR. 0	servation of Freedo ient(s) of Coef. A co	변 6537.082 122.9971 년 년 0	5 4 B cell 0	0 0	0 0	0		
ia. af Oh Jegrees : I Coeffici Ed Err (IR. 0.5	servation of Freedo ient(s) of Coef. A ce 0 2977017	변 6537.082 122.9971 년 년 0	5 4 B cell 0 2603097	0 0 2413290	0 0 2664468	0 234196.3		
to, of Ob Degrees : I Coeffici Rd Err (HR. 0.5 1	servation of Freedo at Coef. A co 2977017 3493647	변 6537.082 122.9971 년 년 0	5 4 B cell 0 2603097 3103185	0 0 2413290 3230110	0 0 2554463 3275647	0 234196.3 162625.1		STD 101 38
to, of Ob Degrees : I Coeffici Std Err (HR. 0.5 1 2	servation of Preedo ient(s) of Coef. A co 2977017 3493647 4959537	변 6537.082 122.9971 년 년 0	5 4 B cell 0 2603097 3103185 4219846	0 0 2413290 3230110 4820048	0 0 2664463 3275647 4666477	0 234196.3 162525.1 320908.8	•	101.38
No. of Ob Degrees : It Coeffici Std Err (HR. 0.5 1 2 4	servation f Preedo ient(s) f Coef. 0 2977017 3493647 4959537 7994378	변 6537.082 122.9971 년 년 0	5 4 B cell 0 2603097 3103185 4219846 6431314	0 0 2413290 3230110 4820048 7474029	0 0 2664463 3275647 4666477 7299907	0 234156.3 162525.1 320908.8 649887.7	•	101.38 72.4195
to, of the Degrees of T Coefficients Std Err of ER. 0 0.5 1 2 4 8	servation f Preedo ient(s) f Coef. 0 2977017 3493647 4959537 7994378 9772500	변 6537.082 122.9971 년 년 0	5 4 B œEI 0 2603097 3103185 4219846 6431314 8217787	0 0 2413290 3230110 4820048 7474029 9304384	0 0 2654463 3275547 4665477 7299907 9098224	0 234196.3 162625.1 320908.8 649887.7 651234.6		101.38 72.4195 140.434
No. of Ob Degrees : It Coeffici Std Err o HR. 0 0.5 1 2 4 8 24	servation f Preedo ient(s) of Coef. 0 2977017 3493647 4959537 7994378 9772500 10647790	변 6537.082 122.9971 년 년 0	5 4 B œli 0 2603097 3103185 4219846 6431314 8217787 8783515	0 0 2413290 3230110 4820048 7474029 9304384 10680735	0 0 2654463 3275647 4666477 7299907 9098224 10037347	0 234156.3 162525.1 320908.8 649887.7 651234.6 886634.9		101_38 72,4195 140,434 284,778
No. of Ob Degrees : It Coeffici Std Err o HR. 0 0.5 1 2 4 8 24 4 8 24	servation f Preedo int(s) f Coef. 0 2977017 3493647 4959537 7994378 9772500 10647790 11437887	변 6537.082 122.9971 년 년 0	5 4 B œll 0 2603097 3103185 4219846 6431314 8217787 8783515 10949407	0 0 2413290 3230110 4820048 7474029 9304384 10680735 11336142	0 0 2654463 3275647 4666477 7299907 9098224 10037347 11257912	0 234196.3 162525.1 320908.8 549887.7 551234.6 886634.9 219096.1		101_38 72.4195 140.434 294.778 288.958
No. of Ob Degrees : It Coeffici Std Err o HR. 0 0.5 1 2 4 8 24 4 8 24	servation f Preedo ient(s) of Coef. 0 2977017 3493647 4959537 7994378 9772500 10647790	변 6537.082 122.9971 년 년 0	5 4 B œli 0 2603097 3103185 4219846 6431314 8217787 8783515	0 0 2413290 3230110 4820048 7474029 9304384 10680735	0 0 2654463 3275647 4666477 7299907 9098224 10037347 11257912	0 234156.3 162525.1 320908.8 649887.7 651234.6 886634.9		101.38 72.4195 140.434 284.778 288.958 390.5752
No. of Ob Degrees : It Coeffici Std Err o HR. 0 0.5 1 2 4 8 24 4 8 24 4 8 72	servation of Preedo init(s) of Coef. 0 2977017 3493647 4959537 7994378 9772500 10647790 11437887 10966207	8 6537.082 122.9071 <u>위</u> 0	5 4 B œll 0 2603097 3103185 4219846 6431314 8217787 8783515 10949407	0 0 2413290 3230110 4820048 7474029 9304384 10680735 11336142	0 0 2654463 3275647 4666477 7299907 9098224 10037347 11257912 10625585	0 234156.3 152525.1 320908.8 649887.7 551234.6 886634.9 219096.1 1025700		101.38 72.4195 140.434 284.778 288.958 390.5752 104.3922
No. of Ob Degrees : It Coeffici Std Err o HR. 0 0.5 1 2 4 8 24 4 8 24 4 8 72 2 70rmulati	servation of Preedo init(s) of Coef. 0 2977017 3493647 4959537 7994378 9772500 10647790 11437887 10966207 on	а 6537.082 122.9071 <u>Л</u> 0 УГ. 3	5 4 8 œli 0 2603097 3103185 4219846 6431314 8217787 8783515 10949407 9232918	0 0 2413290 3230110 4820048 7474029 9304384 10680735 11386142 11677629	0 0 2664463 3275647 7299907 9098224 10037347 11257912 10625585 Date:	0 234196.3 162525.1 320908.8 649887.7 651234.6 886694.9 219096.1 1025700 18/23/90		101.38 72.4195 140.434 284.778 288.958 390.5752
No. of Ob Degrees : I Coeffici Std Err o IIR. 0 0.5 1 2 4 8 24 48 72 24 48 72 24 48 72	servation of Preedo init(s) of Coef. 0 2977017 3493647 4959537 7994378 9772500 10647790 11437887 10966207 on dine	а 6537.082 122.9071 <u>л</u> 0 Яс.\$ 30	5 4 8 cell 0 2603097 3103185 4219846 6431314 8783515 10949407 9232918 "After E-Bea	0 0 2413290 3230110 4820048 7474029 9304384 10680735 11386142 116677529 m sterilization"	0 0 2664463 3275647 7299907 9098224 10037347 11257912 10625585 Date:	0 234156.3 152525.1 320908.8 649887.7 551234.6 886634.9 219096.1 1025700		101.38 72.4195 140.434 284.778 288.958 390.5752 104.3922
Ka. af Oh Degrees : I Coeffici Std Err o HR. 0 0.5 1 2 4 8 24 48 72 24 70rmulati Chlorhesti Propylene	servation of Preedo init(s) of Coef. 0 2977017 3493647 4959537 7994378 9772500 10647790 11437887 10966207 on dine	2 6537.082 122.9071 <u>1</u> 0 57 . 8 30 6	5 4 8 œli 0 2603097 3103185 4219846 6431314 8217787 8783515 10949407 9232918	0 0 2413290 3230110 4820048 7474029 9304384 10680735 11386142 116677529 m sterilization"	0 0 2664463 3275647 7299907 9098224 10037347 11257912 10625585 Date:	0 234196.3 162525.1 320908.8 649887.7 651234.6 886694.9 219096.1 1025700 18/23/90		101.38 72.4195 140.434 284.778 288.958 390.5752 104.3922
No. of Ob Degrees : I Coeffici Std Err o IIR. 0 0.5 1 2 4 8 24 48 72 24 48 72 24 48 72	servation of Preedo init(s) of Coef. 0 2977017 3493647 4959537 7994378 9772500 10647790 11437887 10966207 on dine	а 6537.082 122.9071 <u>л</u> 0 Яс.\$ 30	5 4 8 cell 0 2603097 3103185 4219846 6431314 8783515 10949407 9232918 "After E-Bea	0 0 2413290 3230110 4820048 7474029 9304384 10680735 11336142 116677529 m sterilization"	0 0 2664463 3275647 7299907 9098224 10037347 11257912 10625585 Date:	0 234196.3 162525.1 320908.8 649887.7 651234.6 886694.9 219096.1 1025700 18/23/90		101.38 72.4195 140.434 284.778 288.958 390.5752 104.3922

ELUCION RATE WORKSHEET FOR CHLORMEXIDINE GLUCONATE "A"

TITLE : Chlorheridine Gluconate ADD's S.N. 008031E-PDDS1 Set 2

STANDARD CALIBR	ATION CUI	RVE			1	Data of J	iverage Val	1125	
							की को		
neg/ml AUC	AUC	AVGAUC		Br.				nca/cm2	dif u/cn2
0 0		0		0.0		0.0		0.0	0.0
100 512785		•		0.5		319.6		904.4	
500 2898234				1		472.4			
800 4991913				2		601.7		1736.2	
1000 5603535				4		889.3		2559.3	
2000 12071584				8			1199.1		834.1
				24		1446.8			
				48		1459.9		4233.8	
				72		1448.2		4201.6	-32.2

Regressi	m Output								
Constant		-147175							
Std Err of Y Est		267615.1							
		0.997241							
R Squarec		AM31747							
R Squared No. of Observation	S	6							
No. of Observation		6							
No. of Observation		6							
No. of Observation Degrees of Freedo		6							
No. of Observation Degrees of Freedo X Coefficient(s)	6223.125 163.6756	6	1	C cell		¥¥(i. sto	•	
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef.	6223.125 163.6756 el	6	1	C cæll 0		0	g	•	
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. A c	مس 6223.125 163.6756 طا 0	6 4 B cel 0	0	C	0	0		•	
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. A c 0 0 0.5 1927035 1 3541438	6223.125 163.6756 ell 0 2027821	6 4 B cel 0 1376734 2557354	0	0 1489223 2278756	•	0 1941673 2792516	0 184115.8 541644		<u></u>
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. A c 0 0 0.5 1927035 1 3541439 2 4585628	6223.125 163.6756 ell 0 2027821	6 4 B cel 0 1376734 2557354 3276397	0	0 1489223 2278756 2929749	•	0 1841673 2792516 3597258	0 184115.8 541644 713067.4	•	
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. A c 0 0 0.5 1927035 1 3541439 2 4585628 4 6519381	6223.125 163.6756 ell 0 2027821	6 4 B cel 0 1376734 2557354 3276397 5354612	0	0 1489223 2278756 2929749 4287108	Ţ	0 1841673 2792516 3597258 5387034	0 184115.8 541644 713067.4 911610	•	
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. A c 0 0 0.5 1927035 1 3541439 2 4585628 4 6519381 8 8056236	6223.125 163.6756 ell 0 2027821	6 4 B cel 0 1376734 2557354 3276397	0	0 1489223 2278755 2929749 4287108 6516252	Ţ	0 1841673 2792516 3597258 5387034	0 184115.8 541644 713067.4	•	
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. A c 0 0 0.5 1927035 1 3541439 2 4585628 4 6519381	6223.125 163.6756 ell 0 2027821	6 4 B cel 0 1376734 2557354 3276397 5354612	0	0 1489223 2278756 2929749 4287108	Ţ	0 1841673 2792516 3597258 5387034 7176415 8856139	0 184115.8 541644 713067.4 911610 647598.2 502392.8	•	
No. of Observation Degrees of Preedo I Coefficient(s) Std Err of Coef. HR. A co 0 0 0.5 1927035 1 3541439 2 4585628 4 6519381 8 8056236 24 9508963 48 9385385	에 6223.125 163.6756 테 0 5 2027821	6 4 8 cel 0 1376734 22557354 3276397 5354612 6956756 9772552 8640956	0	0 1489223 2278755 2929749 4287108 6516252 8286903 8786748	·	0 1841673 2792516 3597258 5387034 7176415 5856139 3937696	0 184115.8 541644 713067.4 911610 647598.2 502392.8 322110.4	•	
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. A co 0 0 0.5 1927035 1 3541439 2 4585528 4 6519381 8 8056236 24 9508963	에 6223.125 163.6756 테 0 5 2027821	6 4 8 cel 0 1376734 22557354 3276397 5354612 6956756 9772552	0	0 1489223 2278756 2929749 4287108 6516252 8286903	·	0 1841673 2792516 3597258 5387034 7176415 5856139 3937696	0 184115.8 541644 713067.4 911610 647598.2 502392.8	•	
No. of Observation Degrees of Preedo I Coefficient(s) Std Err of Coef. HR. A co 0 0 0.5 1927035 1 3541439 2 4585628 4 6519381 8 8056236 24 9508963 48 9385385	에 6223.125 163.6756 테 0 5 2027821	6 4 8 cel 0 1376734 22557354 3276397 5354612 6956756 9772552 8640956	0	0 1489223 2278755 2929749 4287108 6516252 8286903 8786748		0 1841673 2792516 3597258 5387034 7176415 8856139 3937696 9864929	0 184115.8 541644 713067.4 911610 647598.2 502392.8 322110.4		
Yo. of Observation Degrees of Preedo I Coefficient(s) Std Err of Coef. HR. A co 0 0 0.5 1927035 1 3541439 2 4585628 4 6519381 8 8056236 24 9508963 48 9385385 72 9169720	е 6223.125 163.6756 е 0 2027821 У1.3	6 4 8 cel 0 1376734 22557354 3276397 5354612 6956756 9772552 8640956	0 1887554	0 1489223 2278755 2929749 4287108 6516252 3286903 8736748 8773646		0 1841673 2792516 3597258 5387034 7176415 8856139 3937696 9864929	G 184115.8 541644 713067.4 911610 647598.2 502392.8 322110.4 221220.7		
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. A c 0 0 0.5 1927035 1 3541439 2 4585628 24 5503963 48 9385385 72 9169720 Formulation Chiorheridine	е 6223.125 163.6756 е 0 2027821 У1.3	6 4 9 0 1376734 2557354 3276397 5354612 6956756 9772552 8640956 8651421 "After E-B	0 1887554	0 1489223 2278755 2929749 4287108 6516252 3286903 8736748 8773646		0 1841673 2792516 3597258 5387034 7176415 8856139 3937696 9864929 Date:	0 184115.8 541644 713067.4 911610 647598.2 502392.8 322110.4 221220.7 08/27/90		
Yo. of Observation Degrees of Freedo I Coefficient(s) Std Err of Coef. HR. & c 0 0 0 0.5 1927035 1 3541439 2 4585628 4 6519381 8 3055236 24 9508963 48 9385385 72 9169720 Formulation	923.125 163.6756 ell 0 2027821 %L% 30	6 4 9 0 1376734 2557354 3276397 5354612 6956756 9772552 8640956 8651421 "3fter: E-B S	0 1287554 eam ster	0 1489223 2278755 2929749 4287108 6516252 3286903 8736748 8773646		0 1841673 2792516 3597258 5387034 7176415 8856139 3937696 9864929 Date:	0 184115.8 541644 713067.4 911610 647598.2 502392.8 322110.4 221220.7 08/27/90		
No. of Observation Degrees of Freedo X Coefficient(s) Std Err of Coef. HR. & c 0 0 0.5 1927035 1 3541438 2 4585628 4 6519381 8 8056236 24 9508963 48 9385385 72 9169720 Formulation Chiorhenidine Fropylene Glycol	6223.125 163.6756 ell 0 2027821 %L3 30 6	6 4 9 0 1376734 2557354 3276397 5354612 6956756 9772552 8640956 8651421 "3fter: E-B S	0 1287554 eam ster	0 1489223 2278755 2929749 4287108 6516252 3286903 8736748 8773646		0 1841673 2792516 3597258 5387034 7176415 8856139 3937696 9864929 Date:	0 184115.8 541644 713067.4 911610 647598.2 502392.8 322110.4 221220.7 08/27/90		

ELUTION RATE WORKSHEET FOR CHLORHENIDINE GLUCONATE "A"

= 238 nm				Data of Average Values dil adj						
ncg/ml	AUC	AUC	AVGAUC	Er.	ncg/ni	mcg/ml	ncg/cm2	dif u/cm2		
0	Û	0	0	0.0	0.0	0.0	0.0	0.0		
100	467687	448195	457941	0.5	334.0	334.0	945.2	945.2		
500	3040010	2886689	2963350	1	496.0	504.4	1427.3	482.2		
800	4782207	4784922	4783565	2	520.1	532.5	1506.9	79.6		
1000	5675335	5459266	5567301	4	717.3	730.3	2066.8	559.9		
2000	12726955	12585654	12656305	8	974.5	992.4	2808.5	74L7		
				24	1305.9	1330.3	3764.7	956.2		
				48	1364.7	1397.4	3954.6	199.9		
				72	1440.4	1474.5	4172.8	218.2		

TITLE : Chlorhenidine Glucomate ADD's B.N. 008031-PDDS1 2 Month Sample § 45 C/ 90% RH

Regression Output:

Constant -218373 "2 Month Sample" Std Err of Y Est 313113.1 R Squared 0.996323 No. of Observations 6 Degrees of Freedom 4

I Coefficient(s) 6304.249 Std Err of Coef. 191.5027

æ.	Å œ	8	Ba	E]	Co	비	AV	3. 9	STD.
0	0	0	0	g	0	0	0	(0
0.5	1776137	1767078	1752691	1655524	2206288	2154971	1887115	215059	.9
1	2501919		2605821		3618084		2908608	503465.	4
2	2601741		3002645		3575465		3060284	400011.	2
4	3250297		4336471		5314697		4303822	83902	3
8	5348750		5605877		6820239		5924955	641705.	1
24	7974299		7654704		8404695		8014566	303438.	9
48	8425247		7619909		9110626		8385261	609239.	1
72	8438032		7722994		10425168		8862065	1143179	9
Porzulati	07.	182.B					Date:	10/29/9	0
Chlorheni	dine	30					<u>71</u> 2	2MSTA-	45
Propylene	Glycal	6							
PEG 300	•	24							
Habrix		40							

ELUTION RATE WORKSHEET FOR CHLORHEXIDINE GLUCONATE "A"

TITLE : Chlorhemidine Gluconate ADD's B.H. 008031-PDDS1 2 Month Sample @ 38 C/90% RH

STANDAR	D CALLER	ATION CO	RVE									
= 238 nm					Data of Average Values dil adj							
ncg/nl	AUC	AUC	AVCAUC	Sr.	ncg/nl	acg/al	ncg/cm2	₫£ u/cm2				
0	0	0	0	· 0.0	0.0	. 0.0	0.0	0.0				
100	626401	622783	624592	0.5	303.2	303.2	858.0	858.0				
500	3037933	3021214	3029574	1	453.1	460.7	1303.8	445.8				
800	5340031	5204862	5272447	2	583.1	594.5	1682.3	378.5				
1000	6333254	6046154	6189709	4	879.3	893.8	2529.5	847.3				
2000	11743334	11517463	11630399	8	1172.3	1194.3	3379.9	850.3				
				24	1397.1	1426.4	4036.7	656.9				
				48	1386.0	1420.9	4021.3	-15.4				
				72	1398.4	1433.1	4055.7	34.4				

Regression Output:

Constant	169858.2 "2 Month Sample"
Std Err of Y Est	280538.4
R Squared	0.996568
No. of Observations	5
Degrees of Freedom	4

I Coefficient(s) 5847.175 Std Err of Coef. 171.5797

R.	1 cei	1	Ba	1	C o	ell	AV	. st).
0	0	0	٥	0	0	0	0	0	
0.5	2125830	2117694	1848705	1728560	1911143	1923725	1942610	141542.9	
1	2520294		3031225		2906785		2819435	168000.2	
2	3363007		3721117		3654393		3579506	155492.3	
4	4953856		5162431		5816949		5311079	367699.5	
8	6677589		6931111		7465099		7024500	328225.6	
24	8017622		8383899		8615243		8338921	246041.9	
48	8108139		3615774		8098531		8274148	241597.9	
72	8296233		8274380		8469823		8346812	87438.24	
Pornulatio	71	XL.					Date:	10/31/90	
Chlorheni	line	30					Pile:	24STA-38	WK1
Propylene	Glycol	6							
PEG 300	-	24							
Matrix		40							

ELUTION RATE WORKSHEET FOR CHLORHEXIDINE GLUCOBATE "A"

TITLE : Chlorhenidine Gluconate ADD's B.M. 008031-PDDS1 2 Month Sample § RT

3	238 nm				Data of A d	verage Va El adj	ues .	
ncg/ml	AUC	AUC	AVGAUC	Hr.	vcg/ni	ncg/nl	mcg/cm2	वेर्म ग/का
0	0	0	0	0.0	0.0	0.0	0.0	0.0
500	3226522	30%717	3161620	0.5	377.6	377.5	1068.6	1068.6
800	5019617	5236543	5128080	1	537.0	546.5	1546.5	477.9
1000	6157377	6295124	6226251	2	617.4	630.8	1785.3	238.8
2000	12265064	12565648	12415356	4	924.8	940.3	2661.0	875.7
				8	1292.7	1315.8	3723.7	1052.7
				24	1606.9	1639.2	4638.9	915.2
				48	1671.0	1711.2	4842.6	203.7
				72	1699.7	1741.5	4929.4	85.8

X.

58610.99 "2 Month Sample" Contrant Sit railist 77878.71 R (parent No. c) (bulevaliuns Degrees: A Desclom 0.999784 5 3

X Coefficient(s) 6194.942 Std Err of Coef. 52.60154

E .	l œ	1	8 a	<u>u</u>	Co	ᆀ	27	3. S	TD.
0	٥	g	0	g	0	0	0	0	
0.5	2279151	2276466	2357340	2254422	2663956	2554740	2397763	156217.	1
1	3026535		3761713		3365010		3385419	300387.5	;
2	3594926		4425371		3630063		3883453	383462.1	
- 4	5079486		6632755		5651642		5787961	641403.8	
8	7827790		9056229		7315886		8066635	730289.3	}
24	10302011		0737379		8999529		10013005	738280.2	
48	9549833		10528555		11152494		10410294	659605.9	ļ
72	12435010		0245774		8982704		10588163	1419696	
formulati	on.	81L-1					Date:	11/1/90	
hiorhen	dine	30					Piler	2MSTA-R	7.7Kl
ropyien	e Glycol	6							
EG 300		24							
latriz		40							

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ELUTION RATE WORKSHEET FOR CHLORHEXIDINE GLUCONATE "A"

TITLE : Chlorhendine Glucomate ADD's B.N. 008031-PDDS1 2 Month Sample & RT Under Water

STANDARD CALLE	NATION CU	RVE							
= 238 nm						Data of J	lverage Val	1985	
							dil adj		
ncg/ni AU	C AUC	AVGAUC		Er.		ncg/ni	nca/nl	nca/cn2	dif u/cm2
0 (0.0		0.0		0.0	0.0
100 62640				0.5		414.5			1173.0
500 303793				1		529.7		1528.5	355.5
800 534003	5204862	5272447		2		676.0	689.2	1950.5	422.0
1000 5333264				4		1053.2			1077.7
2000 1174333				8		1434.4		4133.9	1105.6
				24		1668.4		4823.1	689.2
				48		1704.0	1745.7	4940.4	117.3
				72		1729.1		5013.9	73.5
Regress	ion Cutout	2							
Constant	•	169858.2 '	'2 Month	Sample"					
Sta Err of Y Est		280538.4		•					
R Squared		0.996568							
No. of Observatio	0.5	5							
Degrees of Freed	100	4							
I Coefficient(s)	5847.175	i							
Std Err of Coef.	171.5797	l							
			**						
ER. A	<u>al</u>	8 ce	1	Co	ell	AV(3. STD	•	
0 (0	C	đ	0	0	đ	0		
0.5 242485	5 2323061	3118498	3246501	2275840	2171425	2593530	424662.9		
1 308009	l	3597024		3125047		3267384	233812.7		
2 399426)	4393172		3980116		4122516	191469.8		
4 6684914	I	5969763		6328969		6327882	291960.2		
3 906820	!	9059535		8543785		8557174	411895.4		
24 10040591	ŗ	9885297		9850336		9925410	32690.59		
48 1059799	3	9603919		10198570		10133529	408436.7		
72 10488406	i	10328725		10023552		10280228	192849,3		
Formulation	WLA					finke:	10/21/08		
Chlorheridine	жся 30					Date: Zile:	10/31/90	1971	
Propyiene Giycol	نلا 6						24STA-WT.	87.L	•
Propylene Glycol PEG 300	0 : 24								
Fabrix	40								

84

×:

ELUTION RATE WORKSHEET FOR CHLOREZXIDINE GLUCOSATE "A"

	D CALIER 238 nm	ATION CU	RVE		Data of A	rerage Va El adj	lues	
acg/al	AUC	AUC	AVGAUC	Er.	ncg/nl	ncg/ni	ncg/cn2	äf u/ca2
Ū.	0	0	0	0.0	0.0	ົພ	0.0	0.0
100	626401	622783	624592	0.5	429.5	429.8	1216.3	1216.3
500	3037933	3021214	3029574	1	579.5	590.3	1670.5	454.3
800	5340031	5204862	5272447	2	705.4	719.9	2037.3	365.8
1000	6333261	6046154	6189709	4	1079.2	1096.8	3104.1	1066.7
2000	11974791	12439009	12206500	8	1425.4	1452.4	4110.2	1006.1
				24	1595.5	1631.1	4616.1	505.9
				44	1711.7	1751.6	4957.0	340.9
				77	1597.5	1640.3	4547.1	-114.9

1.7..

TITLE : Chlorhenidine Gluconate ADD's B.M. 008031-PDDS1 2 Month Sample & -40 C

Regression Out	字立
Constant	65627.83 "2 Honth Sample"
Std Err of Y Lst	175155.4
R Squared	0.998775
Ho. of Observations	5
Degrees of Preedom	4

I Coefficient(s) 6120.33 Std Err of Coef. 107.1265

ER.	1 œ	0	8 a		Co	<u>el</u>	y.	G. STD.
0	0	0	ŋ	0	0	Q	0	0
0.5	3005261	3001797	2907659	2908428	2188405	2154476	2596004	369515.4
1	3747506		3869550		3220932		3612663	281440.8
2	4208834		4393063		4546986		4382961	138234.7
4	7330400		6343106		6338632		5570713	466473
3	8921695		9107754		8338855		8789435	327537.3
24	10259998		9456351		9775574		9830641	330390.1
48	11104808		9901390		10619253		10541817	494335.2
72	10357488		9353494		9817388		9842957	410262
?crauiat	ion	肥					Dates	10/30/90
<u>Chlorher</u>	idine	30					File	2NSTA-40.HK
Propyien	e Glyczi	6						
EG 300	-	24						
latrix		40						

ELUTION RATE WORKSHEET FOR SILVER SULPADIALINE "A"

TITLE : 20:10 Silver Sulfadiarine:Chlorberidine Gluconate ADD's 3. N. 003281

STANDARD (TION CUI	RVE						
= 25	4 nm					Data of .	Average Val dil adi	lues	
ncg/ni	AUC	AUC	AVGAUC		Er.	ncg/nl	ncg/ml	ncg/cn2	dif u/cm2
0	0	Q	0		0.0	0.0	0.0	0.0	0.0
1	46372	44364	45368		0.5	- L	4.i	11.7	11.7
5	273436	281165			1	51	5.2	14.8	3.0
10	549823	553172	551498		2	6.2	6.4	18.0	3.2
15	901711	819580	810646		1	1.7		22.4	4.4
					8	9.2		26.7	43
					24	12.5		36.1	9.4
					48	13.5		39.1	3.0
					72	12.1	12.5	35.2	-3.9

	gressio	ı Output:							
			-1175.73						
di dir af	Iz		7979.336						
l Squared			0.999596						
			5						
			3						
legrees of	Preedot	1							
)egrees of Coefficien	Preedon	1 54538.39				·			
legrees of Coefficien	Preedon	1							
)egrees of Coefficien	Preedon	54538.39 633.2009			C cell	7 20	J. STD.		a Na an an
Degrees of Coefficien Std Err of ER. 0	Preedos et(s) Coeé. A cel	54538.39 633.2009	3 		0	a a	G		
legress of Coefficien Std Err of ER. 0 0.5	Preedor et(s) Coeé A cel 0 214448	54538.39 633.2009 1	3 B ceil 0 255063	0	0 205355	0 0 224955.3	0 21610.56		
Coefficien Stater of ER. 0.5 1 :	Precion et(s) Coef A cel 0 214448 252974	54538.39 633.2009 1	3 B cell 0 255063 320957	0	0 205355 249534	0 0 224955.3 277821.7	G 21610.56 30990.87	•	
legrees of Coefficien Rd Err of IR. 0.5 1 2	Preedon et(s) Coef. A cel 0 214448 252974 323430	54538.39 633.2009 1	3 B cell 0 255063 320957 390370	0	0 205355 249534 301459	0 0 224955.3 277821.7 338419.7	C 21610.56 30990.87 37813.66	•	
Coefficient Stat Err of HRL 0.5 1 : 2 : 4 :	Pression et(s) Cost. 0 214448 252974 323430 423496	54538.39 633.2009 1	3 B ceil 0 255063 320957 390370 479151	0	0 205355 249534 301459 361092	0 0 224955.3 277821.7 338419.7 421246.3	0 21610.56 30990.87 37813.66 48223.63	•	
Coefficient Statistic af URL 0.5 1 : 2 : 4 : 9 :	Pression ett(s) Cosé A cel 0 214448 262974 323430 423496 519375	54538.39 633.2009 1	3 B ceil 0 255063 320957 390370 479151 574044	0	0 205355 249534 301459 361092 415254	0 0 224955.3 277821.7 338419.7 421246.3 502891	0 21610.56 30990.87 37813.66 48223.63 65865.31	•	
Degrees of Coefficient Std Err of IRL 0 0.5 1 2 4 8 24	Pression ett(s) Cosé. 0 214448 262974 323430 423496 519375 740342	54538.39 633.2009 1	3 B ceil 0 255063 320957 390370 479151 574044 713775	0	0 205355 249534 301459 361092 415254 590990	0 0 224955.3 277821.7 338419.7 421246.3 502891 581702.7	0 21610.56 30990.87 37813.66 48223.63 65865.31 65585.31	•	
Degrees of Coefficient Std Err of IR. 0 0.5 1 2 4 4 8 24 24 48	Preedot tt(s) Coef 0 214448 262974 323430 423496 519375 740342 759709	54538.39 633.2009 1	3 B cell 0 255063 320957 390370 479151 574044 713776 670700	0	0 205355 249534 301459 361092 415254 590990 776738	0 0 224955.3 277821.7 338419.7 421246.3 502891 581702.7 735715.7	0 21610.56 30990.87 37813.66 48223.63 65865.31 65865.31 65053.97 46495.69	•	
Degrees of Coefficient Std Err of IR. 0 0.5 1 2 4 4 8 24 24 48	Pression ett(s) Cosé. 0 214448 262974 323430 423496 519375 740342	54538.39 633.2009 1	3 B ceil 0 255063 320957 390370 479151 574044 713775	0	0 205355 249534 301459 361092 415254 590990	0 0 224955.3 277821.7 338419.7 421246.3 502891 581702.7 735715.7	0 21610.56 30990.87 37813.66 48223.63 65865.31 65585.31	•	
Coefficients of Coefficients Std Err of ER. 0 0.5 1 2 4 4 3 2 4 4 5 72 5	Preedot et(s) Coeé 214448 262974 323430 423496 519375 740342 759709 566635	54538.39 633.2009 1	3 B cell 0 255063 320957 390370 479151 574044 713776 670700	0	0 205355 249534 301459 361092 415254 590990 776738	0 0 224955.3 277821.7 338419.7 421246.3 502891 581702.7 735715.7	0 21610.56 30990.87 37813.66 49223.63 65865.31 65053.97 46495.69 17275.85	•	
Coefficients of Coefficient Sch Err of ER. 0 0.5 1 2 4 4 4 3 2 4 5 2 4 5 2 4 5 2 4 5 2 4 5 2 4 5 2 4 5 2 4 5 7 2 4 5 7 2 4 5 7 2 4 5 7 7 2 4 5 7 7 7 8 1 2 7 7 8 1 2 7 7 8 1 2 7 7 8 1 2 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 8 1 7 7 7 7	Preedot et(s) Coeé 214448 262974 323430 423496 519375 740342 759709 568635	54538.39 633.2009 1	3 B ceil 0 255063 320957 390370 479151 574044 713776 670700 674797	0	0 205355 249534 301459 361092 415254 590990 776738	0 0 224955.3 277821.7 338419.7 421246.3 502891 581702.7 735715.7 559630.3	0 21610.56 30990.87 37813.66 48223.63 65865.31 65865.31 65053.97 46495.69		
Coefficient Sch Err of ER. 0 0.5 1 2 4 4 3 24 72 4 3 24 72 4 3 24 72 4 3 24 72 24 24 72 24 24 72 24 24 72 24 24 72 24 24 72 24 27 24 27 27 24 27 27 24 27 27 27 27 27 27 27 27 27 27 27 27 27	Preedot tt(s) Coeć A cel 0 214448 262974 322430 423496 519375 740342 759709 568635 diazine	54538.39 633.2009 1 0	3 B ceil 0 255063 320957 390370 479151 574044 713776 670700 674797 HL 3	0	0 205355 249534 301459 361092 415254 590990 776738	0 0 224955.3 277821.7 338419.7 421246.3 502891 681702.7 735715.7 6559630.3 Date:	0 21610.56 30990.87 37813.66 49223.63 65865.31 65053.97 46495.69 17275.85 12/12/90		
Coefficient Std Err of IR. 0 0.5 1 2 4 4 8 24 72 4 8 72 4 8 72 6 72 6 72 6 72 6 72 72 72 72 72 72 72 72 72 72 72 72 72	Preedot tt(s) Coeć A cel 0 214448 262974 322430 423496 519375 740342 759709 568635 diazine	54538.39 633.2009 1 0	3 B ceil 0 255063 320957 390370 479151 574044 713776 670700 674797 HLA 20	0	0 205355 249534 301459 361092 415254 590990 776738	0 0 224955.3 277821.7 338419.7 421246.3 502891 681702.7 735715.7 6559630.3 Date:	0 21610.56 30990.87 37813.66 49223.63 65865.31 65053.97 46495.69 17275.85 12/12/90		
0.5 1 : 2 : 4 : 24 : 24 :	Preedot tt(s) Coeć A cel 0 214443 262974 323430 423496 519375 740342 759709 568635 diazine te giuco	54538.39 633.2009 1 0	3 B ceil 0 255063 320957 390370 479151 574044 713776 670700 674797 HLA 20 10	0	0 205355 249534 301459 361092 415254 590990 776738	0 0 224955.3 277821.7 338419.7 421246.3 502891 681702.7 735715.7 6559630.3 Date:	0 21610.56 30990.87 37813.66 49223.63 65865.31 65053.97 46495.69 17275.85 12/12/90		

ELUTION RATE WORKSHEET FOR CELOREEXIBLE GLUCOBATE "A"

TITLE : 2010 Silver Sulfadiarine Chlorbendine Gluconate ADD's B. N. 003281

:	238 cm			Data of Average Values dil adj						
ncg/nl	AUC	ACC	AVGAUC	Er.	ncg/ni	ncg/nl	mcg/cm2	čif u/cal		
0	0	0	0	0.0	0.0	0.0	0.0	0.0		
100	619520	600716	610118	0.5	362.2	362.2	1025.1	1025.1		
500	3117956	3120785	3119371	1	504.7	513.8	1454.1	429.0		
800	4985128	4794929	4890029	2	630.2	642.8	1819.2	365.2		
1000	6071163	6017421	6044292	4	740.8	756.6	2141.1	321.9		
				1	767.4	785.9	2224.1	83.0		
				24	841.8	861.0	2436.5	212.4		
				48	822.4	843.5	2397.1	-49.4		
				n	804.2	824.8	2334.2	-52.9		

Regression Outy	out:
Constant	20430.12
Std Err of Y Est	48658.43
R Squared	0,999742
No. of Observations	5
Degrees of Preedom	3

I Coefficient(s) 6067.358 Std Err of Coef. 56.27254

ER.	1 œ	1	8 a	IJ	Co	리	74). S
0	0	0	0	0	0	0	0	0
0.5	2402738	2341651	2378828	2227049	1987059	1971724	2218175	177647
1	3636005		2922089		2690685		3082926	402334
2	4315594		3604970		3612031		3844198	33339.5
- 4	4891292		4199381		4455056		4515243	285£59.5
8	5113108		4327639		4588378		4576375	326647.6
24	5490682		4823725		5068778		5127728	275456.3
48	5525816		4624003		4881577		5010465	379276.3
72	5012750		4805380		4882066		4900055	85609.82
reulati	20		WL.S				Date:	09/05/90
ilte si	fadiazine		20				<u>Ple:</u>	5003281.
hiorieni	dine gluca	nate	10					
EG 300	-		16					
ropylene	gircal		4					
latrix	• -		50					

ELUTION RATE WORKSHEET FOR CLINDANYCIN PHOSPHATE "A"

TITLE : Batch No. 007121 - 20% Clindamycin 10% Chlorheridine

STANDAR	D CALIER	ATION CU	IRVE									
:	194 nm				Data of A	verage Va	lues					
ncg/nl	AUC	AUC	AVGAUC		dil adj							
0	0	0	0	Hr.	ncg/nl	ncg/nl	mcg/cm2	₩ u/ca2				
100	3400978	3384284	3392631	0.0	0.0	0.0	0.0	0.0				
500	18201675	18505687	18353681	0.5	492.3	492.3	1393.2	1393.2				
800	31495347	31354622	31424985	1	788.0	800.3	2264.9	871.7				
1000	38863552	36557727	37710640	2	998.4	1018.1	2881.2	616.2				
2000	73198389	76087102	74642746	4	1376.1	1401.0	3965.0	1083.5				
				8	1720.4	1754.8	4966.0	1001.1				
				24	2043.9	2086.9	5905.9	939.8				
				49	2115.4	2166.5	6131.3	225.5				
				72	2045.5	2098.4	5938.6	-192.7				

							فالأرجب وبعذوب صارح فالأقري
Regre	ssion Out	ut:					
Constant		82658.69					
Std far af I I	st	781243.6					
R Squared		0.999351					
No. of Observa	tions	6		-			
Degrees of Fre	edon	4					
3 Coefficient(s) 37505	53					
Std Err of Coe	,						
ER.	1 cell	8 0	1	C cell	ŸĆ	i. std.	
0	0	0 0	0	a a	•	Û	
-	•	• •	•		10547500	•	
			19959203 206966			2607572	
1 22972		32958402	329858			4714063	
2 30781		39285106	425189		37528452	4950252	
4 49291		53034363	527588		51694777	1703367	
8 68344	013	63626434	618537		64608067	•	
24 83044	821	73066549	741113	13	76740904	4477903	
48 83528	541	75184481	795635	12	79425518	3407846	
72 82061	854	71589171	767627	30	76804585	4275557	
Formulation	Ŵ	.1			Date:	08/31/90	
Cindanyan		20			File	B007121.WK1	
Chlorieridine		10					
Propylene giyo	d	5					
PEG 300	-	24					
Oligoner		40					
		••					

ELUTION RATE WORKSHEET FOR CHLORHEXIDINE GLUCONATE "A"

TITLE : Dual Loaded ADD's - E. N. 007121

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		ATION CU.	RVE							
2	238 ne						Data of i	Average Val		
								dil adj		
ncg/nl			AVGAU	C	<u>Ľ</u> .		•••	ncg/ni		
0	-	Q	0		0.0		0.0		0.0	0.0
100		498858	496954		0.5		635.3		1797.9	1797.9
	2818823				1		685.0			185.7
	4877314				2		754.2			
1000	5910123	5765662	5837893		- 4		840.9			
					1		936. 3			
					24		995.4			172.3
					48		1019.4			
					n		1009.1	1034.6	2927.9	-27.4
	Regressio	z Outpuż								
Constant			-54938.6							
	rf I Est		93817.74							
l Square	d		0.999001							
•										
la. af 01	servation	-	5							
la. af 01	servation: of Preedo:	-								
la, af Ob Jegrees (af Prædo:	1	5							
la, af Ok Jegrees () Coeffic	of Preedo: ient(s)	n 5940.064	53							
la, af Ok Jegrees () Coeffic	af Prædo:	n 5940.064	53							
la, af Ok Jegrees () Coeffic	of Preedo: ient(s)	n 5940.064 108.4761	53	 £]	C c	el	YAC	i. std.		
ia. af Ob Degrees (Coeffic Rd Err (of Preedo ient(s) sf Coef.	n 5940.064 108.4761	5 3	- <u>1</u>	с. с.	ell 0	AVG	;. STD. O		
la. af Oh Jegrees (Coeffic Rd Err (HR. 0	of Preedo: ient(s) of Coef. A ce 0	n 5940.064 108.4761 II 0	5 3 8 ce 0 3553819	0	0 3365412	0	0 3713816	0 402051.8		
la. af Oh Jegrees (Coeffic Rd Err (HR. 0.5 1	zf Preedo: ient(s) zf Coef. A ce 4256829 3924889	n 5940.064 108.4761 II 0	5 3 5 œ 0	0	0	0	0 3713815 4014217	0 402051.8 63200.29		
la. af Ok Degrees (Coeffic Rd Err (HR. 0.5 1 2	zf Preedo: ient(s) zf Coef. A ce 0 4256829 3924889 4190742	n 5940.064 108.4761 II 0	5 3 8 ce 0 3553819	0	0 3365412	0	0 3713815 4014217	0 402051.8 63200.29 167078.6		
la. af Ok Degrees (Coeffic Rd Err (HR. 0.5 1 2 4	zf Preedo: ient(s) zf Coef. 0 4256829 3924889 4190742 4943758	2 5940.064 108.4761 1 1 0 4303754	5 3 8 ce 0 3553819 4056274 4517753 4951045	0	0 3365412 4061488	0	0 3713815 4014217	0 402951.8 63200.29 167078.6		
la. af Ok Jegrees (K Coeffin Rd Err (HR. 0 0.5 1 2 4 8	zf Preedo: ient(s) zf Coef. A ce 0 4256829 3924889 4190742 4943758 5705545	2 5940.064 108.4761 1 1 0 4303754	5 3 8 ce 0 3553819 4056274 4517753 4951045 5451328	0	0 3365412 4061488 4567359	0	0 3713816 4014217 4425295 4939995 5510141	0 402051.8 63200.29 167078.6 10389.1 141773.4	- 	
la. af Ok Jegrees (K Coeffin Rd Err (HR. 0 0.5 1 2 4 8	zf Preedo: ient(s) zf Coef. 0 4256829 3924889 4190742 4943758	2 5940.064 108.4761 1 1 0 4303754	5 3 8 ce 0 3553819 4056274 4517753 4951045	0	0 3365412 4061488 4567359 4925181	0	0 3713816 4014217 4425295 4939995	0 402051.8 63200.29 167078.6 10389.1 141773.4		
la. af Ob begrees (Coefficient Rd Err (HR. 0 0.5 1 2 4 8 24	zf Preedo: ient(s) zf Coef. A ce 0 4256829 3924889 4190742 4943758 5705545	2 5940.064 108.4761 1 1 0 4303754	5 3 8 ce 0 3553819 4056274 4517753 4951045 5451328	0	0 3365412 4061488 4567359 4925181 5373549	0	0 3713816 4014217 4425295 4939995 5510141	0 402051.8 53200.29 167078.6 10889.1 141773.4 144951.1		
la. af Ob begrees (Coeffic Rd Err (HR. 0 0.5 1 2 4 8 24 4 8 24	zf Preedo: ient(s) xf Coef. A co 4256829 3924889 4190742 4943758 5705545 6057370	2 5940.064 108.4761 1 1 0 4303754	5 3 8 ce 0 3553819 4056274 4517753 4951045 5451328 5797642	0	0 3365412 4061488 4567359 4925181 5373549 5717821	0	0 3713815 4014217 4425295 4939995 5510141 5857611	0 402051.8 63200.29 167078.6 10389.1 141773.4 144361.1 213448		
Ic. of Ob Degrees (Rd Err (Rd Err (0.5 1 2 4 8 24 48 72 (ormulat)	zf Preedo: ient(s) zf Coef. A coef. 0 4256829 3924889 4190742 4943758 5705545 6057370 6185209 5917217 cm	n 5940.064 108.4761 II 0 4303754	5 3 8 œ 0 3553819 4056274 4517753 4951045 5451328 5797642 5701277	0	0 3365412 4061488 4567359 4925181 5373549 5717821 6114642	0	0 3713816 4014217 4425295 5510141 5857611 6000376 5939311	0 402051.8 63200.29 167078.6 10389.1 141773.4 144361.1 213448	- 	
Ia. of Ob Degrees (Rd Err (HR. 0 0.5 1 2 4 8 24 48 72 (ormulati hlorber)	zf Preedo: ient(s) zf Coef. A coef. 0 4256829 3924889 4190742 4943758 5705545 6057370 6185209 5917217 on dine gluco	n 5940.064 108.4761 II 0 4303754	5 3 8 œ 0 3553819 4056274 4517753 4951045 5451328 5797642 5701277 5866702 WL 3	0 3457800	0 3365412 4061488 4567359 4925181 5373549 5717821 6114642	0	0 3713816 4014217 4425295 5510141 5857611 6000376 5939311	0 402051.8 63200.29 167078.6 10889.1 141773.4 144341.1 213448 70069.15		
Ic. of Ob Degrees (Rd Err (Rd Err (0.5 1 2 4 8 24 48 72 (ormulat)	zf Preedo: ient(s) zf Coef. A coef. 0 4256829 3924889 4190742 4943758 5705545 6057370 6185209 5917217 on dine gluco	n 5940.064 108.4761 II 0 4303754	5 3 8 œ 0 3553819 4056274 4517753 4951045 5451328 5797642 5701277 5866702 WL 3	0 3457800	0 1365412 4061488 4567359 4925181 5373549 5717821 6114642 6034015	0	0 3712816 4014217 4425295 4939995 5510141 5857611 6000376 5939311 Date:	0 402951.8 63200.29 167078.6 10889.1 141773.4 144941.1 213448 70059.15 03/15/90		
Ia. of Ob Degrees (Rd Err (HR. 0 0.5 1 2 4 8 24 48 72 (ormulati hlorber)	zf Preedo: ient(s) zf Coef. A coef. 0 4256829 3924889 4190742 4943758 5705545 6057370 6185209 5917217 on iine gluce iin 904	n 5940.064 108.4761 II 0 4303754	5 3 8 cm 0 3553819 4056274 4517753 4951045 5451328 5797642 5701277 5866702 WL & 10 5 20 6	0 3457800	0 1365412 4061488 4567359 4925181 5373549 5717821 6114642 6034015	0	0 3712816 4014217 4425295 4939995 5510141 5857611 6000376 5939311 Date:	0 402951.8 63200.29 167078.6 10889.1 141773.4 144941.1 213448 70059.15 03/15/90		
Ic. of Ob Degrees (Rd Err (Rd Err (HR. 0 0.5 1 2 4 8 24 48 72 (ormulat. hlorber) finiany:	zf Preedo: ient(s) zf Coef. A coef. 0 4256829 3924889 4190742 4943758 5705545 6057370 6185209 5917217 on iine gluce iin 904	n 5940.064 108.4761 II 0 4303754	5 3 8 ce 0 3553819 4056274 4517753 4951045 5451328 5797642 5701277 5866702 WL 3 10 5 29	0 3457800	0 1365412 4061488 4567359 4925181 5373549 5717821 6114642 6034015	0	0 3712816 4014217 4425295 4939995 5510141 5857611 6000376 5939311 Date:	0 402951.8 63200.29 167078.6 10889.1 141773.4 144941.1 213448 70059.15 03/15/90		

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ELUTION RATE WORKSHEET FOR CHLORMENIDINE GLUCONATE "A"

TITLE : Triple Loaded ADD's - B. N. 007132

STANDAR											
-		NTION CU	RVE								
:	238 nm						Data of	Average Val	ues		
								dii adj			
ncg/nl	AUC	70C	AVGAU	C	Er.		ncg/ni	ncg/nl	mcg/cm2	čif u/cm2	
0	0	0	0		0.0		0.	0.0	0.0	0.0	
100			456954		0.5		411.			1165.2	
500	2818823	2851914	2835369		1		502.5	512.9	1451.4	286.2	
	4877314				2		563.0	575.6	1528.5	177.5	
1000	5910123	5765662	5837893		- 4		678.	692.1	1958.7	329.8	
					8		859.1	876.1	2479.2	520.5	
					24		973.9	995.4	2815.9	337.7	
					48		1040.4	1064.7	3013.1	196.2	
					72		1012.5	1038.6	2939.3	-73.8	
	8										
Constant	Regressio		: -54938.6								
Std Err			93817.74								
R Square			0.999001								
	n Servation:		v.372001 5								
	of Freedom		3								
Jegrees											
T Conffic	innile	5040 064									
I Coeffici		5940.064 108 4761									
I Coeffici Std frr (5940.064 108.4761									
		108.4751) cz	4	Co	<u></u>	AV	3. STD.	•	*****	
Std frr (HR.	at Coet. A ce	103.4751 11	1 02						,	*****	
Std Err (ER. 0	of Coef. A ce	108.4751 11 0	B 02	- 0	J	0	0	0	•		
Std frr (IR. 0 0.5	of Coef. A ce 0 2592736	108.4751 11 0	B cz 0 2289575	- 0	J 2384224	0	0 2390762	0 137555.7		****	
Std Err (of Coef. A ce 0 2592736 3134542	108.4751 11 0	B ce 0 2289575 2833810	- 0	J 2384224 2762829	0	0 2390762 2930394	0 137555.7 189015.6	•	*****	
Std frr (HR. 0 0.5 1 2	of Coef. A ce 2592736 3194542 3546674	108.4751 11 0	B ce 0 2289575 2833810 3097431	- 0	J 2384224 2762829 3224257	0	0 2390762 2930394 3289454	0 137555.7 189015.6 189108.1		*****	
Std frr (IR. 0 0.5 1 2 4	of Coef. A ce 0 2592736 3134542	108.4751 11 0	B ce 0 2289575 2833810 3097431 3760579	- 0	J 2384224 2762829	0	0 2390762 2930394 3289454 3972793	0 137555.7 189015.5 189108.1 181611.7			
Std Err (ER. 0 0.5 1 2 4 8	d Coef. A ce 0 2592736 3194542 3546674 4204192 5331058	108.4751 11 0	B ce 0 2289575 2833810 3097431 3760579 4903182	- 0	J 2384224 2762829 3224257 3953507 4910395	0	0 2390762 2930394 3289454 3972793 5048212	0 137555.7 189015.6 189108.1 181611.7 200924.2			
Std Err c ER. 0 0.5 1 2 4 8 24	at Coet. A ce 0 2592736 3194542 3546674 4204192 5331058 6007229	108.4751 11 0	B ce 0 2289575 2833810 3097431 3760579 4903182 5614689	- 0	J 2384224 2762829 3224257 3953507 4910395 5568386	0	0 2390762 2930394 3289454 3972793 5048212 5730101	0 137555.7 189015.6 189108.1 181611.7 200024.2 196868.5			
Std Err c ER. 0 0.5 1 2 4 8 24 48	d Coef. A ce 0 2592736 3194542 3546674 4204192 5331058	108.4751 11 0	B ce 0 2289575 2833810 3097431 3760579 4903182	- 0	J 2384224 2762829 3224257 3953507 4910395	0	0 2390762 2930394 3289454 3972793 5048212 5730101 6124946	0 137555.7 189015.6 189108.1 181611.7 200924.2			
Std Err (A Ceef. A Ce 0 2592736 3194542 3546674 4204192 5331053 6007229 6465892 5464653	108.4751 11 0	B ce 0 2289575 2833810 3097431 3760579 4903182 5614689 6035336 5528767	- 0	J 2384224 2762829 3224257 3953507 4910395 5568386 5869309	0 2237471	0 2390762 2930394 3285454 3972793 5048212 5730101 6124846 5959985	0 137555.7 189015.6 189103.1 181611.7 200024.2 196856.5 253224.5 385587.7			
Std Err (ER. 0 0.5 1 2 4 8 24 48 72 Formulatin	A Ceef. A Ce 0 2592736 3194542 3546674 4204192 5331058 6007229 6465892 5466653 on	103.4761 11 0 2556690	B ce 0 2289575 2833810 3097431 3760579 4903182 5614689 6035336 5528767 WL 1	0 2283873	J 2384224 2762829 3224257 3953607 4910395 5568386 5869309 5886536	0 2237471	0 2390762 2930394 3289454 3972793 5048212 5730101 6124846 5959985 Date:	0 137555.7 189015.6 189103.1 181611.7 200924.2 196863.5 253224.5 385587.7 08/16/90			
Std Err (ER. 0 0.5 1 2 4 8 24 48 72 Formulatin Chlorheri	a ce a ce 0 2592736 3194542 3546674 4204192 5331058 6007229 6465892 5466653 on dine glucc	103.4761 11 0 2556690	B ce 0 2289575 2833810 3097431 3760579 4903182 5614689 6035336 5528767 WE 1 10 1	0 2283873	J 2384224 2762829 3224257 3953507 4910395 5568386 5869309	0 2237471	0 2390762 2930394 3285454 3972793 5048212 5730101 6124846 5959985	0 137555.7 189015.6 189103.1 181611.7 200024.2 196856.5 253224.5 385587.7			
Std Err of HR. 0 0.5 1 2 4 8 24 48 72 Formulatin Chlorheri Clindanyr	A ce 0 2592736 3194542 3546674 4204192 5331058 6007229 6465892 5466653 on dine giuco in P04	103.4761 EI 2556690	B ce 0 2289575 2833810 3097431 3760579 4903182 5614689 6035336 5528767 WL 1 10 1	0 2283873	J 2384224 2762829 3224257 3953607 4910395 5568386 5869309 5886536	0 2237471	0 2390762 2930394 3289454 3972793 5048212 5730101 6124846 5959985 Date:	0 137555.7 189015.6 189103.1 181611.7 200924.2 196863.5 253224.5 385587.7 08/16/90			
Std Err of HR. 0 0.5 1 2 4 8 24 4 8 72 Formulatin Chlorhenir Clindanyc Siver sult	A Ce A Ce 2592736 3134542 3546674 4204192 5331053 6607229 6469892 5466653 on dine gluco tin PO4 fadiatine	103.4761 EI 2556690	B ce 0 2289575 2833810 3097431 3760579 4903182 5614689 6035336 5528767 Ht. 3 10 10	0 2283873	J 2384224 2762829 3224257 3953607 4910395 5568386 5869309 5886536	0 2237471	0 2390762 2930394 3289454 3972793 5048212 5730101 6124846 5959985 Date:	0 137555.7 189015.6 189103.1 181611.7 200924.2 196863.5 253224.5 385587.7 08/16/90			
Std Err of HR. 0 0.5 1 2 4 8 24 48 72 Formulatin Chlorheri Clindanyr	A Ce A Ce 2592736 3134542 3546674 4204192 5331053 6607229 6469892 5466653 on dine gluco tin PO4 fadiatine	103.4761 EI 2556690	B ce 0 2289575 2833810 3097431 3760579 4903182 5614689 6035336 5528767 WL 1 10 1	0 2283873	J 2384224 2762829 3224257 3953607 4910395 5568386 5869309 5886536	0 2237471	0 2390762 2930394 3289454 3972793 5048212 5730101 6124846 5959985 Date:	0 137555.7 189015.6 189103.1 181611.7 200924.2 196863.5 253224.5 385587.7 08/16/90			

ELUTION RATE WORKSHEET FOR CHLOREEXIDINE GLUCONATE "A"

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TITLE : 12:Silver sulfadiasine 10:Chlorhenidine gluconate 12:Clindanycin phosphate ADD's B. N. 009101

STANDAR	d Calibri	ntion cu	XV2		•					
:	238 nm						Data of I	Average Val dil adij	lues	
ncg/nl	AUC	YOC	AVGAUC		Ħr.		ncg/ni		ncq/cn2	र्ट्ेा ग∕ त्य2
0	0	0	0		0.0				00	0.0
100	543954	582546	563250		0.5		157.2	157.3	445.1	445.1
500	3043792	3021822	3032807		1		318.1	322.0	911.2	466.2
900	5037611	4945711	4991661		2		439.5	447.5	1266.4	355.2
1000	6440265	6038695	6239481		4		514.0	525.0	1485.8	219.4
2000			ERR		8		592.4	605.3	1712.9	227.1
					24		771.4	786.2		512.0
					48		913.5	932.7	2639.7	414.7
					n		913.3	936.1	2549.2	9.5
Constant	Regressio	ם טעקים	- 4 3212.2							
Std Err :	€ ¥ 2.+		45744.65							
	للاستلك		13/11.03							
. Courses										
R Square	đ		0.999786							
lo, at Ob Degrees (d servation: £ Preedor	8	0.999786 5 3							
lo. at ob	d servation: £ Preedor ient(s)	-	0.999786 5 3							
lo, af Ob Degrees (I Coeffici	d servation: £ Preedor ient(s)	n 6268.025 52.89194	0.999786 5 3	 L	د C	 el	740). STD.	•	
io, af Ob Degrees (I Coeffic Std Zrr (d servation: £ Preedon ient(s) £ Coef.	n 6268.025 52.89194	0.999786 5 3	. 0	د ی د ی	 eli 0	0 VA(3. STD. 0		
io, of Ob Degrees (I Coeffici Std Zrr (HR. 0	d servation: sf Freedor ient(s) sf Coef. A ce	n 6258.025 52.89194 Ti	0.999786 5 3 B cel		0	0	0			
io, of Ob Degrees of K Coeffici Std Zrr (HR. 0 0.5	d servation: f Preedon ient(s) f Coef. A ce 0	n 6258.025 52.89194 Ti	0.999786 5 3 B ceil	0	0	0	0 942550.5	0		
No. of Ob Degrees (T Coeffici Std Zrr (HR. 0 0.5 1	d servation: f Freedon f Coef. A ce 0 1123941	n 6258.025 52.89194 Ti	0.999786 5 3 B œil 0 924679	0	0 845810	0	0 942550.5 1950378	0 163887.5		
No. of Ob Degrees (K Coeffici Std 2rr (HR. 0 0.5 1 2	d servation: f Freedou ient(s) f Coef. A ce 0 1123941 1780202	n 6258.025 52.89194 Ti	0.999786 5 3 B ceil 0 924679 1975496	0	0 845810 2095435	0	0 942550.5 1950378 2711793	0 163387.5 129913.2		
No. of Ob Degrees (K Coeffici Std Zrr (KR. 0 0.5 1 2 4	d servation: f Freedor ient(s) f Coef. A ce 0 1123941 1780202 2619822	n 6258.025 52.89194 Ti	0.999786 5 3 B cell 0 924679 1975496 2625362	0	0 845810 2095435 2885695	0	0 942550.5 1950378 2711793 3178764	0 163387.5 129913.2 123035.6		
Io. of Ob Degrees of K Coeffici Std Zrr o HR. 0 0.5 1 2 4 8	d servation: f Freedon f Coef. A ce 0 1123941 1780202 2619822 2212764	n 6258.025 52.89194 Ti	0.999786 5 3 8 cei 0 924679 1975496 2625362 3017220	0	0 845810 2095435 2885695 3306309	0	0 942550.5 1950378 2711793 3178764	0 163387.5 129913.2 123035.6 120443.9		
No. of Ob Degrees of K Coeffici Std Zrr of HR. 0 0.5 1 2 4 8 24	d servation: f Preedon f Coef. A ce 0 1123941 17802C2 2619822 2212764 3872845	n 6258.025 52.89194 Ti	0.999786 5 3 8 cell 0 924679 1975496 2629362 3017220 3459905	0	0 845810 2095435 2885695 3306309 3677736	0	0 942550.5 1950378 2711793 3178764 3670162 4791979	0 163887.5 129913.2 123035.6 120443.9 163667.1		
No. of Ob Degrees of Std Zrr of HR. 0 0.5 1 2 4 8 24 4 8 24	d servation: f Preedon f Coef. A ce 0 1123941 1780202 2619822 2212764 3872845 5485600	n 6258.025 52.89194 Ti	0.999786 5 3 8 cell 0 924679 1975496 2629362 3017220 3459905 4406463	0	0 845810 2095435 2885695 3306309 3677736 4483875	0	0 942550.5 1950378 2711793 3178764 3670162 4791979 5632388	0 163387.5 129913.2 123035.6 120443.9 163667.1 491481		
No. of Ob Degrees of Std Zrr of HR. 0 0.5 1 2 4 8 24 4 8 24	d servation: f Preedon ient(s) f Coef. 0 1123941 1780202 2619822 2212764 3872845 5485600 6107414 5879506	n 6258.025 52.89194 Ti	0.999786 5 3 8 cell 0 924679 1975496 2629362 3017220 3459905 4406463 5293579	0	0 845810 2095435 2885695 3306309 3677736 4483875 5646170	0 785822	0 942550.5 1950378 2711793 3178764 3670162 4791979 5632388	0 163387.5 129913.2 123035.6 120443.9 153667.1 491481 333232.3		
No. of Ob Degrees of Std Zrr of HR. 0 0.5 1 2 4 8 24 4 8 24 48 72 20rnulatii	d servation: f Preedon ient(s) f Coef. 0 1123941 1780202 2619822 2212764 3872845 5485600 6107414 5879506	n 6268.025 52.89194 II 0 1199616	0.999786 5 3 8 cell 0 924679 1975496 2629362 3017220 3459905 4406463 5293579	0	0 845810 2095435 2885695 3306309 3677736 4483875 5646170	0 785822	0 942550.5 1950378 2711793 3178764 3670162 4791979 5632388 5681129	0 163287.5 129913.2 123035.6 120443.9 168667.1 491481 333222.3 148205.8	 -	
No. of Ob Degrees of Std Zrr of HR. 0 0.5 1 2 4 8 24 4 8 24 48 72 20rnulatii	d servation: f Preedon f Coef. A cee 0 1123941 1780202 2619822 2519842 2212764 3872845 5485600 6107414 5879506 on fadiasine	n 6268.025 52.89194 II 0 1199616	0.999786 5 3 8 cell 0 924679 1975496 2629362 3017220 3459905 4406463 5293579	0	0 845810 2095435 2885695 3306309 3677736 4483875 5646170	0 785822	0 942550.5 1950378 2711793 3178764 3670162 4791979 5682388 5681129 Date:	0 163287.5 129913.2 123035.6 120443.9 168667.1 491481 333232.3 148205.8 19/11/90	 -	
Io. of Ob Degrees of Std Zrr of HR. 0 0.5 1 2 4 8 24 48 72 Formulatin Sliver sui	d servation: f Preedon f Coef. A cee 0 1123941 1780202 2619822 2212764 3872845 5485600 6107414 5879506 on fadiasine iine	n 6268.025 52.89194 11 0 1199616 #8.8 12	0.999786 5 3 8 cell 0 924679 1975496 2629362 3017220 3459905 4406463 5293579	0	0 845810 2095435 2885695 3306309 3677736 4483875 5646170	0 785822	0 942550.5 1950378 2711793 3178764 3670162 4791979 5682388 5681129 Date:	0 163287.5 129913.2 123035.6 120443.9 168667.1 491481 333232.3 148205.8 19/11/90		
Io. of Ob Degrees of Std Zrr of HR. 0 0.5 1 2 4 8 24 48 72 Formulatin Silver suithorheri	d servation: f Preedon f Coef. A cee 0 1123941 1780202 2619822 2212764 3872845 5485600 6107414 5879506 cn fadiarine in phos.	а 6268.025 52.89194 1199616 1199616 же. в 12 10	0.999786 5 3 8 cell 0 924679 1975496 2629362 3017220 3459905 4406463 5293579	0	0 845810 2095435 2885695 3306309 3677736 4483875 5646170	0 785822	0 942550.5 1950378 2711793 3178764 3670162 4791979 5682388 5681129 Date:	0 163287.5 129913.2 123035.6 120443.9 168667.1 491481 333232.3 148205.8 19/11/90		

~4

ELUTION RATE WORKSHEET FOR SILVER SULFADIAZINE "A"

4.4

TITLE : 20:10 Silver sulfadiarine:Chlorhenidine Gluconate ADD's 3.M. 010181-PDDS2 Set 1

TANDARD	CALIERA	TION CUR	VE							
= 2	54 nm					Data of	Averagi dil adj		25	
ncg/nł	AUC	AUC	AVGAUC		Ħr.	mcq/m	acq/		ncg/cn2	dif u/cm2
0	0	0	0		0.0	0.	<u>ן</u>	0.0	0.0	0.0
1	47448	49780	48614		0.5	2	9	29	83	83
5	281594	286471	284033		1	4.2		43	12.1	3.8
10	568117	576598	572358		2	6.4		65	18.3	6.1
15	833426	847205	840315		4	9.3		9.4	26.5	8.3
					8	11.		15	32.5	5.9
					24	12.5	1	2.4	35.2	2.8
					48	14.) 1	13	40.5	5.3
					72	13.0	1	4.2	40.0	-0.5
l Squared			0.99968							
io. of Obs	ervations f Preedoz ent(s)		3							
ia. af Obs Jegrees a Coefficie	ervations f Preedoz ent(s)	56524.58 584.1306			C cell	AV	·G.	STD.		****
ia. af Obs Jegrees a Coefficie Stal Err a HR. 0	ervations E Preedon ent(s) E Coef. A cei O	56524.58 584.1306	3 9 ceil 0	0	0	. 0 0	1	0		
ia. of Obs Jegrees of Coefficies Stal Err of HR.	ervations f Preedom nt(s) f Coef. A cei 0 172125	36524.58 584.1306	3 8 ceil 0 162597	•	0 160724	0 0 165148.	7 4991.	0 924		*******
ia. af Obs Jegrees a Stal Err a HR. 0 0.5 1	ervations Freedom ant(s) E Coef. A cei 0 172125 232959	36524.58 584.1306	3 8 cell 0 162597 251906		0 160724 225010	0 0 165149. 236958.	7 4991. I 1094	0 924 3.7		
ia. af Obs Jegrees a Stal Err a HR. 0.5 1 2	ervations E Preedom ent(s) E Coef. A cei 0 172125 232959 354554	36524.58 584.1306	3 8 cell 0 162597 251906 360935	-	0 160724 225010 358230	0 0 165148. 236958. 357906.2	7 4991. 1094 3 2615.0	0 924 3.7 267		
ia. of Obs legrees of Stal Err of HR. 0.5 1 2 4	ervations E Preedon ent(s) E Coef. A cei 0 172125 232959 354554 523156	36524.58 584.1306	3 8 cell 0 162597 251905 360935 510231		0 160724 226010 358230 526826	0 0 165148. 236958. 357906. 520071	7 4991. 1094 3 2615.0 7117.4	0 924 3.7 067		<u></u>
ia. of Obs legrees of Std Err of HR. 0.5 1 2 4 8	ervations E Preedon ent(s) E Coef. A cei 0 172125 232959 354554 523156 649196	36524.58 584.1306	3 B cell 0 162597 251906 360935 510231 675252	-	0 160724 226010 358230 526826 577233	0 00 165149. 236958. 357906. 520071 633893.	7 4991 1094 3 2615.0 7117.4 4145	0 924 3.7 067 116 3.2		*******
ia. of Obs legrees of Stal Err of HR. 0 0.5 1 2 4 8 24	ervations f ?reedom at(s) f Coef. 0 172125 232959 354554 523156 649196 694514	36524.58 584.1306	3 B ceil 0 162597 251906 360935 510231 675252 703979	-	0 160724 226010 358230 526826 577233 659998	0 0 165148. 236958. 357906. 520071 633893. 686163.	7 4991 1094 2615.0 7117.4 117.4 18901	0 924 3.7 067 116 3.2 .11		********
ia. of Obs legrees of Stal Err of HR. 0 0.5 1 2 4 8 24 43	ervations f Preedon ent(s) f Coef. 0 172125 232959 354554 523156 649196 694514 837370	36524.58 584.1306	3 B ceil 0 162597 251906 360935 510231 675252 703979 741313		0 160724 226010 358230 526826 577233 659998 792565	0 0 165149. 236958. 357906. 520071 633893. 686163.7 790416	7 4991. 1094 2615.0 7117.4 4145 18901 39244.	0 924 3.7 067 116 3.2 .11 .54		****
ia. of Obs legrees of Stal Err of HR. 0 0.5 1 2 4 8 24	ervations f ?reedom at(s) f Coef. 0 172125 232959 354554 523156 649196 694514	36524.58 584.1306	3 B ceil 0 162597 251906 360935 510231 675252 703979		0 160724 226010 358230 526826 577233 659998	0 0 165148. 236958. 357906. 520071 633893. 686163.	7 4991. 1094 3 2615.0 7117.4 4145 18901 39244.	0 924 3.7 067 116 3.2 .11 .54		
ia. of Obs legrees of Coefficies Sol Err of HR. 0 0.5 1 2 4 8 24 48 72 Yormulatio	ervations f Preedom ent(s) f Coef. 0 172125 232959 354554 523156 649196 649196 649196 649196 649196 837370 759865 n	36524.58 584.1306	3 B ceil 0 162597 251906 360935 510231 675252 703979 741313 815255 HL \$		0 160724 226010 358230 526826 577233 659998 792565	0 0 165148. 236958. 357906. 520071 633893. 686163. 790416 778700 Date:	7 4991. 1094 2615.0 7117.4 18901 39244. 25852 11/26/	0 924 3.7 067 116 3.2 .11 .54 2.3		
ia. of Obs legrees of Coefficies Sol Err of HR. 0 0.5 1 2 4 8 24 48 72 Yormulatio Silver sulf	ervations f Preedom at(s) f Coef. 0 172125 232959 354554 523156 649196 649196 649196 649196 649196 649196 649196 649196 649196 649196 649196 649196 649196 649196 649196 649196 649196 759865 n	3 56524.58 584.1306 1 0	3 B ceil 0 162597 251906 360935 510231 675252 703979 741313 815255 WL 1 20		0 160724 226010 358230 526826 577233 659998 792565	0 0 165148. 236958. 357906. 520071 633893. 686163. 790416 778700	7 4991. 3 2615.0 7117.4 4145 718901 39244. 25855	0 924 3.7 067 116 3.2 .11 .54 2.3		
ia. of Obs legrees of Coefficies Stal Err of HR. 0 0.5 1 2 4 8 24 43 72 Pormulatio Silver sull Shiorhenio	ervations f Preedom at(s) f Coef. 0 172125 232959 354554 523156 649196 694514 837370 759865 n fadiazine ine gluco	3 56524.58 584.1306 1 0	3 B cell 0 162597 251906 360935 510231 675252 703979 741313 815255 HL 1 20 10		0 160724 226010 358230 526826 577233 659998 792565	0 0 165148. 236958. 357906. 520071 633893. 686163. 790416 778700 Date:	7 4991. 1094 2615.0 7117.4 18901 39244. 25852 11/26/	0 924 3.7 067 116 3.2 .11 .54 2.3		
ia. of Obs legrees of Coefficies Sol Err of HR. 0 0.5 1 2 4 8 24 48 72 Yormulatio Silver sulf	ervations f Preedom at(s) f Coef. 0 172125 232959 354554 523156 649196 694514 837370 759865 n fadiazine ine gluco	3 56524.58 584.1306 1 0	3 B ceil 0 162597 251906 360935 510231 675252 703979 741313 815255 WL 1 20		0 160724 226010 358230 526826 577233 659998 792565	0 0 165148. 236958. 357906. 520071 633893. 686163. 790416 778700 Date:	7 4991. 1094 2615.0 7117.4 18901 39244. 25852 11/26/	0 924 3.7 067 116 3.2 .11 .54 2.3	<u> </u>	

ELUTION RATE WORKSHEET FOR SULPADIALINE "A"

TITLE :	20:10 51	er sulfadiazine:Chlorhezidine	Gluconate ADD's	B.J.	010181-PDDS2 Set 2
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é .

= 254 nm	ON CURVE		Data of Average Vi dil adj	ive
ncg/nl AUC	AUC AVGAUG	Ēr.	acg/ni acg/ni	ncg/cn2 dif u/cn2
0 0	0 0	0.0	0.0 0.0	•••
	49780 48614	0.5	27 27	
	86471 284033	1	ត ព	
	76598 572353	2	រ ឆ	16.8 4.5
	47205 840316	4	9.0 9.2	
		8	11.6 11.8	
		24	12.8 13.1	
		48	14.3 14.6	
		'n	12.8 13.1	37.2 -4.2
Regression (Cutput:		ی ہے ہیں میں اور بی ایک پر میں اور	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,
Constant	-1388.49			
Std Err of Y Est	7360.973			
9 Squared	0.99963			
No. of Observations	5			
Degrees of Freedom				
neaters of Liggroup	3			
-	3			
I Coefficient(s) 56	524.58			
I Coefficient(s) 56				
I Coefficient(s) 56	524.58	l Cœi	I AVG. ST).
I Coefficient(s) 56 Std Zrr of Coef. 58	524.58 4.1306	1 C cei 0 0	1 AVG. ST 0 0 0).
I Coefficient(s) 56 Std Irr of Coef. 58 ER. A ceil	524.58 4.1306 B ce).
I Coefficient(s) 56 Std Irr of Coef. 58 ER. A ceil 0 0	524.58 4.1306 5 cei 0 0	0 0	0 0 0).
I Coefficient(s) 56 Std Irr of Coef. 58 ER. A cell 0 0 0.5 156481	524.58 4.1306 B cei 0 0 149805	0 0 144629	0 0 0 0 150305 4851.459).
I Coefficient(s) 56 Std 2rr of Coef. 58 ER. A cell 0 0 0.5 156481 1 256043	524.58 4.1306 9 0 149605 230484	0 0 144629 233125	0 0 0 150305 4851.459 239884 11476.9).
I Coefficient(s) 56 Std 2rr of Coef. 58 ER. A cell 0 0 0.5 156481 1 256043 2 335883	524.58 4.1306 0 0 149605 230484 313159	0 0 144629 233125 333666	0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76).
I Coefficient(s) 55 Std Zrr of Coef. 58 ER. A cell 0 0 0.5 156491 1 256043 2 335883 4 521096	524.58 4.1306 0 0 149805 230484 313159 501791	0 0 144629 233125 333666 505004	0 0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76 509297 8445.636).
I Coefficient(s) 55 Std Zrr of Coef. 58 ER. A cell 0 0 0.5 156491 1 256043 2 335883 4 521096 8 668402	524.58 4.1306 0 0 149805 230484 313159 501791 657800	0 0 144629 213125 333666 505004 631563	0 0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76 509297 8445.636 652538.3 15484.38).
X Coefficient(s) 55 Std Zrr of Coef. 58 ER. A cell 0 0 0.5 156481 1 256043 2 335883 4 521096 8 668402 24 865599	524.58 4.1306 0 0 149805 230484 313159 501791 657900 503376	0 0 144629 233125 333666 305004 631563 704010	0 0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76 509297 8445.636 652538.3 15484.38 724328.3 108011.9).
I Coefficient(s) 56 Std 2rr of Coef. 58 ER. A cell 0 0 0.5 156481 1 256043 2 335883 4 521096 8 668402 24 865599 48 383498 72 785088	524.58 4.1306 0 0 149805 230484 313159 501791 657800 603376 747036 667302	0 0 144629 233125 333666 505004 631563 704010 785088	0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76 509297 8445.636 652588.3 15484.38 724328.3 108011.9 806874 59770.93 720977 48648.96).
I Coefficient(s) 56 Std 2rr of Coef. 58 ER. A cell 0 0 0.5 156481 1 256043 2 335883 4 521096 8 668402 24 865599 48 383498 72 785088 Formulation	524.58 4.1306 0 0 149805 230484 313159 501791 657800 603376 747036 667302 HL 3	0 0 144629 233125 333666 505004 631563 704010 785088	0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76 509297 8445.636 652538.3 15484.38 724328.3 108011.9 806874 59770.93 720977 48648.96 Date: 11/25/90	
I Coefficient(s) 56 Std 2rr of Coef 58 ER. A cell 0 0 0.5 156481 1 256043 2 335883 4 521096 8 668402 24 865599 48 388498 72 785088 Formulation Silver sulfadianne	524.58 4.1306 9 0 149805 230484 313159 501791 657800 603376 747036 567302 911.1 20	0 0 144629 233125 333666 505004 631563 704010 785088	0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76 509297 8445.636 652588.3 15484.38 724328.3 108011.9 806874 59770.93 720977 48648.96	
I Coefficient(s) 56 Std 2rr of Coef 58 ER. A cell 0 0 0.5 156481 1 256043 2 335883 4 521096 8 668402 24 865599 48 388499 72 785088 Formulation Silver sulfadiatine Chlorhendine glucona	524.58 4.1306 9 0 0 149605 230484 313159 501791 657800 603376 747036 567302 Ht.% 20 te i0	0 0 144629 233125 333666 505004 631563 704010 785088	0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76 509297 8445.636 652538.3 15484.38 724328.3 108011.9 806874 59770.93 720977 48648.96 Date: 11/25/90	
X Coefficient(s) 56 Std Zrr of Coef. 58 ER. A cell 0 0 0.5 156481 1 256043 2 335883 4 521096 8 668402 24 865599 48 388498 72 785088	524.58 4.1306 9 0 149805 230484 313159 501791 657800 603376 747036 567302 911.1 20	0 0 144629 233125 333666 505004 631563 704010 785088	0 0 0 150305 4851.459 239884 11476.9 327569.3 10229.76 509297 8445.636 652538.3 15484.38 724328.3 108011.9 806874 59770.93 720977 48648.96 Date: 11/25/90	

ELUTION RATE WORKSHEET FOR CHLORHENIDINE GLUCONATE "A"

TITLE : 20:10 Silver Sulfadiarine: Chlorheridine Glucmate ADD's B.N. 010181-PPDS2 Set 1

		ATION CU	4V2							
:	238 cm							iverage Vali	25	
ncg/nl	AUC	AUC	AVGAUC		Ēr.			dii adj acq/ni		dif u/cm2
1000 1000 1000	AUC 0		ATGAUC		ш. QQ		0.0 0.0		1.0 0.0	0.0
-	-	501975	•		0.5		110.1		311.6	311.6
		3056439			1		147.6		425.5	114.0
		4817120			2		213.4		614.5	188.9
		5857809			4		320.3			307.0
					9		441.0		1270.8	349.3
200	12004014	12281809	17140747		24		508.8		1471.2	200.4
					29 48		300.5 747.5		2151.4	680.2
					10 72		762.1		2209.7	58.3
					14		104.4	100.0	<u> </u>	
	Regressio	n Output								
ionstant			-25235.2							
	f I Est		82715.82							`
Square	a servation	_	0.999722							
ם א נות	1. 1. 1 1 1 A 14 A 14	5	6							
	مليسين ک	-	•							
	f ?reedo	1	4							
legrees (4							
iegrees (Coeffici	ient(s)	5062.321	4							
iegrees (Coeffici	ient(s)		4							
iegrees (Coeffici	ient(s)	5062.321 50.58969	4	1	C o		740	i. std.		
egrees (Coeffici tid Err (HR. 0	ient(s) of Coef. A ce	5062.321 50.58969 네 0	4 	- 0	0	0	0	0		
egrees (Coeffici Ed Err (ER. 0 0.5	ient(s) of Coef. A ce 0 779832	5062.321 50.58969 비	4 B cei 0 522647	-	0 629037	0	0 642318.2	0 94262.71		
egrees (Coeffici ted Err (HR. 0 0.5 1	<u>ient(s)</u> f Coef. A ce 0 779832 1008822	5062.321 50.58969 네 0	4 B cei 0 522647 795491	- 0	0 629037 805256	0	0 642318.2 869856.3	0 94262.71 98344.4		
egrees (Coefficient Ed Err (HR. 0 0.5 1 2	<u>ient(s)</u> £ Coef. A ce 0 779832 1008822 1522727	5062.321 50.58969 네 0	4 B cei 0 522647 795491 1140880	- 0	0 629037 905256 1142635	0	0 642318.2 869856.3 1268747	0 94262.71 98344.4 179592.2		
egrees (Coeffici ted Err (HR. 0 0.5 1 2 4	ient(s) fc Coef. A ce 0 779832 1008822 1522727 2177481	5062.321 50.58969 네 0	4 B cei 0 522647 795491 1140880 1766784	- 0	0 629037 805256 1142635 1805256	0	0 642318.2 869856.3 1268747 1916507	0 94262.71 98344.4 179592.2 185203.7		
egrees (Coefficient Err (HR. 0 0.5 1 2 4 8	ient(s) f Coef. A ce 0 779832 1008822 1522727 2177481 2875241	5062.321 50.58969 네 0	4 B cei 0 522647 795491 1140880 1766784 2532709	- 0	0 629037 805256 1142635 1805256 2537589	0	0 642318.2 869856.3 1268747 1916507 2648513	0 94262.71 98344.4 179592.2 185203.7 160333.3		
egrees (Coefficient Ed Err (HR. 0 0.5 1 2 4 8 24	ient(s) f Coef. A ce 0 779832 1008822 1522727 2177481 2375241 4070036	5062.321 50.58969 네 0	4 B cei 0 522647 795491 1140880 1766784 2532709 2577678	- 0	0 629037 805256 1142635 1805256 2537589 2530707	0	0 642318.2 869856.3 1268747 1916507 2648513 3059474	0 94262.71 98344.4 179592.2 185203.7 160333.3 714832.7		
Egrees of Coefficients of Coef	ient(s) f Coef. A ce 0 779832 1008822 1522727 2177481 2375241 4070036 4568508	5062.321 50.58969 네 0	4 B cei 0 522647 795491 1140880 1766784 2532709 2577678 4689061	- 0	0 629037 805256 1142635 1805256 2537589 2530707 4261474	0	0 642318.2 869856.3 1268747 1916507 2648513 3059474 4506348	0 94262.71 98344.4 179592.2 185203.7 160333.3 714832.7 130010.4		
Egrees of Coefficients of Coef	ient(s) f Coef. A ce 0 779832 1008822 1522727 2177481 2375241 4070036	5062.321 50.58969 네 0	4 B cei 0 522647 795491 1140880 1766784 2532709 2577678	- 0	0 629037 805256 1142635 1805256 2537589 2530707	0	0 642318.2 869856.3 1268747 1916507 2648513 3059474 4506348	0 94262.71 98344.4 179592.2 185203.7 160333.3 714832.7		
Egrees of Coefficients of Coef	ient(s) f Coef. A ce 0 779832 1008822 1522727 2177481 2375241 4070036 4568509 4662512	5062.321 50.58969 네 0	4 B cei 0 522647 795491 1140880 1766784 2532709 2577678 4689061	- 0	0 629037 805256 1142635 1805256 2537589 2530707 4261474	0	0 642318.2 869856.3 1268747 1916507 2648513 3059474 4506348 4595000 Date:	0 94262.71 98344.4 179592.2 185203.7 160333.3 714832.7 130010.4		
egrees of Coefficient ted Err of HR. 0 0.5 1 2 4 9 24 4 8 72 24 48 72	ient(s) f Coef. A ce 0 779832 1008822 1522727 2177481 2375241 4070036 4568509 4662512	5062.321 50.58969 HI 0 754990	4 B cei 0 522647 795491 1140880 1766784 2532709 2577678 4689061 4695151	- 0	0 629037 805256 1142635 1805256 2537589 2530707 4261474	0	0 642318.2 869856.3 1268747 1916507 2648513 3059474 4506348 4595000 Date:	0 94262.71 98344.4 179592.2 185203.7 160333.3 714832.7 180010.4 119302.1		
egrees (Coeffici ted Err (HR. 0 0.5 1 2 4 8 24 48 72 'ormulati ilver sui	ient(s) f Coef. A ce 0 779832 1008822 1522727 2177481 2375241 4070036 4568508 4662512 on	5062.321 50.58969 HI 0 754990	4 B cei 0 522647 795491 1140880 1766784 2532709 2577678 4689061 4695151 ¥2.3	- 0	0 629037 805256 1142635 1805256 2537589 2530707 4261474	0	0 642318.2 869856.3 1268747 1916507 2648513 3059474 4506348 4595000 Date:	0 94262.71 98344.4 179592.2 185203.7 160333.3 714832.7 180010.4 119302.1 11/12/90		
egrees (Coeffici ted Err (HR. 0 0.5 1 2 4 8 24 48 72 'ormulati ilver sui	ient(s) f Coef. A ce 0 779832 1008822 1522727 2177481 2875241 4070036 4568508 4662512 on Ifadiazine áine gluco	5062.321 50.58969 HI 0 754990	4 B cei 0 522647 795491 1140880 1766784 2532709 2577678 4689061 4695151 ¥2.3 20	- 0	0 629037 805256 1142635 1805256 2537589 2530707 4261474	0	0 642318.2 869856.3 1268747 1916507 2648513 3059474 4506348 4595000 Date:	0 94262.71 98344.4 179592.2 185203.7 160333.3 714832.7 180010.4 119302.1 11/12/90		

ELUTION RATE WORKSHEET FOR CHLORHETIDINE GLUCOHATE "A"

MILE : 20:10 Silver SulfadiarinesChlorhenidine Gluconate ADD's B.R. 010181-PPD52 Set 2

TAYDAR :	D CALIBR 238 nm						Data of i	lverage Val	lues	
								वेरी क्यों		
acg/al	AUC	AUC	AVGAUC	:	Hr.		ncg/nl		ncg/cn2	! dif u/cm2
0	0	. 0	0		20		Ĵu	•	0.0	۵۵
100	655604	501975	578790		0.5		87.5	87.5	247.8	247.8
500	2989292	3056439	3022866		1		127.8	129.9	367.7	<u>119.9</u>
800	4953288	4817120	4885204		2		181.9	192.0	543.5	175.8
			5892700		4		295.9	300.5	850.7	307.2
2000	12004574	12281809	12143242		8		413.3			339.8
					24		608.4	618.7	1751.0	560.6
					48		691.8	707.0	2000.9	249.9
			•		n		707.5	724.8	2051.3	50.4
	Regressio	n Output	••••••••••••				• • • • • • • • • • • • • • • • • • • •			
ionstant	•	•	-25235.2							
td Brr :	f y Est		82715.82							
Square			0.999722							
Square		5								
Square a. of Ob	d		0.999722							
Square a. of Ob egrees o	d servation of Preedo	2	0.9997 <u>22</u> 5 4							
Square a. of Oh egrees of Coefficient	d servation of Freedo uent(s)	5052 <u>.321</u>	0.999722 5 4							
Square a. of Oh egrees of Coefficient	d servation of Freedo uent(s)	2	0.999722 5 4							
Square a. of Oh egrees of Coefficient	d servation of Freedo uent(s)	5052 <u>.321</u> 50.58969	0.999722 5 4		C c	 el	PAC.	5. STD	•	
Square a. of Oh egrees of Coeffici td Err o	d servation of Preedo uent(s) of Coef.	5052 <u>.321</u> 50.58969	0.999722 5 4 B ce	11	C c	 eil 0	0 VVC	5. STD. 0	•	
Square a. of Ob egrees of Coeffici td Err of HR.	d servation of Preedo ent(s) of Coef. A co 0	5052.321 50.58969	0.999722 5 4 B ce		0	0	0		•	
Square a. af Ob egrees a Coeffici td Err o HR. G	d servation of Preedo ent(s) of Coef. A co 0	5052.321 50.58969 <u>1</u>	0.999722 5 4 B ce 0	Q	0	0	0 505695.2	Q	•	
Square a. of Ob egrees of Coeffic td Err of HR. G 0.5 1	d servation of Preedo ent(s) of Coef. A ca 0 409141	5052.321 50.58969 <u>1</u>	0.999722 5 4 B ce 634469	Q	0 450776	0	0 505695.2 749227.3	0 93731.6		
Square a. of Ob egrees of td Err of HR. G 0.5 1 2	d servation of Preedo ent(s) of Coef. A ce 0 409141 840500	5052.321 50.58969 <u>1</u>	0.999722 5 4 B ce 634469 792349	Q	0 450776 614833	0	0 505695.2 749227.3	0 93731.6 97042.97		
Square a. of Ob egrees of td Err of HR. 0.5 1 2 4	d servation of Freedo ent(s) of Coef. A ce 0 409141 840500 1121776	5052.321 50.58969 <u>1</u>	0.999722 5 4 B ce 0 634469 792349 1176662	Q	0 450776 614833 1060535	0	0 505695.2 749227.3 1119658 1768426	0 93731.6 97042.97 47432.31	•	
Square o. of Ob egrees of Coeffic td Err o HR. G 0.5 1 2 4 8	d servation of Freedo ent(s) of Coef. A ce 0 409141 840500 1121776 1792132	5052.321 50.58969 <u>1</u>	0.999722 5 4 B ce 0 634469 792349 1176662 1730964	Q	0 450776 614833 1060535 1782181	0	0 505695.2 749227.3 1119658 1768426	0 93731.6 97042.97 47432.31 26799.1 29832.79	•	
Square a. of Ob egrees of Coefficients td Err of HR. G 0.5 1 2 4 8 24	d servation of Freedo ent(s) of Coef. A ce 0 409141 840500 1121776 1792132 2517837	5052.321 50.58969 <u>1</u>	0.999722 5 4 B ce 0 634469 792349 1176662 1730964 2444906	Q	0 450776 614833 1060535 1782181 2477399	0	0 505695.2 749227.3 1119658 1768426 2480047	0 93731.6 97042.97 47432.31 26799.1 29832.79 123037.4	•	
Square a. of Ob egrees of Coefficients td Err of HR. G 0.5 1 2 4 8 24 43	d servation of Preedo ent(s) of Coef. A ce 0 409141 840500 1121776 1792132 2517837 3495559	5052.321 50.58969 <u>1</u>	0.999722 5 4 8 œ 0 634469 792349 1176662 1730964 2444906 3706013	Q	0 450776 614833 1050535 1782181 2477399 3787610	0	0 505695.2 749227.3 1119658 1768426 2480047 3663060 4168843	0 93731.6 97042.97 47432.31 26799.1 29832.79 123037.4		
Square a. of Ob egrees of Coefficients td Err of HR. G 0.5 1 2 4 8 24 43	d servation of Preedo ent(s) of Coef. A ce 0 409141 840500 1121776 1792132 2517837 3495559 3993441 4160022	5052.321 50.58969 <u>1</u>	0.999722 5 4 8 œ 0 634469 792349 117662 1730964 244906 3706013 4271955	Q	0 450776 614833 1060535 1782181 2477399 3787610 4241134	0 437715	0 505695.2 749227.3 1119658 1768426 2430047 3663060 4168843 4264067	0 93731.6 97042.97 47432.31 25799.1 29832.79 123037.4 124664.8	•	
Square o. of Ob egrees of Coefficient td Err of HR. 0.5 1 2 4 8 24 48 72 ormulacio	d servation of Preedo ent(s) of Coef. A ce 0 409141 840500 1121776 1792132 2517837 3495559 3993441 4160022	5052.321 50.58969 <u>1</u>	0.999722 5 4 8 ce 0 634469 792349 1176662 1730964 2444906 3706013 4271955 4405738	Q	0 450776 614833 1060535 1782181 2477399 3787610 4241134	0 437715	0 505695.2 749227.3 1119658 1768426 2430047 36633060 4168843 4264067 Date:	0 93731.6 97042.97 47432.31 25799.1 23832.79 123037.4 124664.8 103781.3		
Square a. of Ob egrees of Coefficient td Err of HR. C 0.5 1 2 4 8 24 48 72 crmulation liver sul	d servation f Preedo ent(s) f Coef. A ce 0 409141 840500 1121776 1792132 2517837 3495559 3993441 4160022 m	व्य 5052.321 50.58969 <u>ग</u> 0 464261	0.999722 5 4 8 ce 0 634469 792349 1176662 1730964 2444906 3706013 4271955 4405738 WL \$	Q	0 450776 614833 1060535 1782181 2477399 3787610 4241134	0 437715	0 505695.2 749227.3 1119658 1768426 2430047 36633060 4168843 4264067 Date:	0 93731.6 97042.97 47432.31 25799.1 23832.79 123037.4 124664.8 103781.3 11/12/90		
Square a. of Ob egrees of Coefficient td Err of HR. C 0.5 1 2 4 8 24 48 72 crmulation liver sul	d servation f Freedo ent(s) f Coef. A ce 0 409141 840500 1121776 1792132 2517837 3495559 3993441 4160022 m fadiazine tine gluco	व्य 5052.321 50.58969 <u>ग</u> 0 464261	0.999722 5 4 8 ce 0 634469 792349 117662 1730964 2444906 3705013 4271955 4405738 ¥218 20	Q	0 450776 614833 1060535 1782181 2477399 3787610 4241134	0 437715	0 505695.2 749227.3 1119658 1768426 2430047 36633060 4168843 4264067 Date:	0 93731.6 97042.97 47432.31 25799.1 23832.79 123037.4 124664.8 103781.3 11/12/90		

APPENDIX V

IN VIVO DATA SHEETS

90 EFFICACY OF ANTIMICROBIAL DERMAL DRESSINGS FOR PREVENTING INFECTION CONTAMINATED FULL THICKNESS SKIN EXCISION WOUNDS ON GUINEA PIGS

	LNOSA	SUCCESS RATR		4/5 5/6	-	
2	P. AKRUGINOSA		55.5 X 10 ² 51.4 X 10 ²	6.8 X 10 ³ 52.8 X 10 ³	1.5 X 10 ⁰	
FFAMINAN	IREUS	SUCCESS RATE		6/6 5/5		4/4
ACTERIAL CON	STAPH. AUREUS	COUNT	55.9 X 10 ¹ 51.2 X 10 ³	52.4 X 10 ² 51.0 X 10 ²	272 X 10 ¹	52.2 X 10 ² 4/4
		SUCCESS RATE ³	5/5	5/5		
	STREP. PYOGENES	COUNT ²	1.0 x 10 ²	54.0 X 10 ²		
		FORMULATION ¹	30Chlik 10Chlik/20AgSdz	/ lochlx/loAgsdz/loClind	buttont/znefwoz (27Gent/20Cl ind ⁴

EFFICACY OF ANTIMICROBIAL DERNAL DRESSINGS FOR TREATING INFECTED FULL THICKNESS SKIN EXCISION WOUNDS ON GUINEA PIGS

	K SON	RATE	0/5 0/5	0/5	
	P. ARRUGINOSA	COUNT	$\begin{array}{c} 8.9 \times 10^{7} \\ 2.1 \times 10^{7} \end{array}$	1.5 X 10 ⁷	
TERIA	IREUS	RATE	5/5 2/4	5/5 3/4	.4/5
INPECTING BACTERIA	STAPH. AUREUS	COUNT	52.5 X 10 ² 2.3 X 10 ⁵	51.3 X 10 ⁴ 1.8 X 10 ⁴ 6.1 X 10 ⁴	9.6 X 10 ² 4/5
Ħ	COGENES	RATE	5/5	5/5	
	STREP. PYOGENES	COUNT ²	51.1 X 10 ²	51.2 X 10 ²	
	-	FORMULATION ¹	30Chlik/20AgSdz	lochlx/loAgsdz/loclind 51.2 X 10 ² 20Agsdz/luclind	27Gent/20Clind ⁴

- Expressed as **% w/v with drug abbreviation (e.g., 30ChlHx is 30% chlorhexidine** gluconate. AgSdz is silver sulfadiazine, Clind is clindamycin phosphate and Gent is gentamicin sulfate. gluconate. 4
 - Count is expressed as colony forming units of bacteria per gram of tissue (CFU/ ~
 - q) and was calculated as the antilog of the mean of the log counts. Success rate is the number of wounds with 2<10³ CFU/g per total number of wounds that were treated. ň
- Results from experiments done in 1989 (i.e., not with the new batch of 12 mil thick dressings. +

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Z #:9177 888 119 .

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APPENDIX VI

TABLE OF DELIVERIES

No.	Formulation	Delivered	Date
1	Chlorhexidine 30/30/40	25	11-17-89
2	Chlorhexidine 30/6/24/40 (6 mils)	45	11-17-89
3	Chlorhexidine 30/6/24/40 (20 mils) 45	11-17-89
4	Chlorhexidine 30/6/24/40 (16 mils) 45	12-15-89
5	Chlorhexidine 30/6/24/40 (12 mils) 45	02-15-90
6	Chlorhexidine/ 10/20/30/40 Silver sulfadiazine	45	04-04-97
7	Placebos	45	04-04-90
8	Chlorhexidire/ 10/10/10 Silver sulfadiazine/Clindamycin	45	07-20-90
9	Silver sulfadiazine/ 20/10 Clindamycin	45	07-20-90
10	Chlorhexidine/ 10/20 Clindamycin	45	07-20-90
11	Chlorhexidine 2.5" x 2.5"	200	08-16-90
J 2	Chlorhexidine 1" x 1"	100	08-16-90
13	Placebos	100	08-16-90
14	Chlorhexidine/ 10/12/12 Silver sulfadiazine/Clindamycin	45	09-12-90
15	Chlorhexidine/ 10/20 Silver sulfadiazine	200	11-01-90
16	Placebos	100	11-01-90
17	Chlorhexidine/ 10/10/10	25	11-09-90
18	Adhesive dressings	200	N/D

Year 3

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