CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-756

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

FEB 1 1999

Clinical Pharmacology/Biopharmaceutics Review

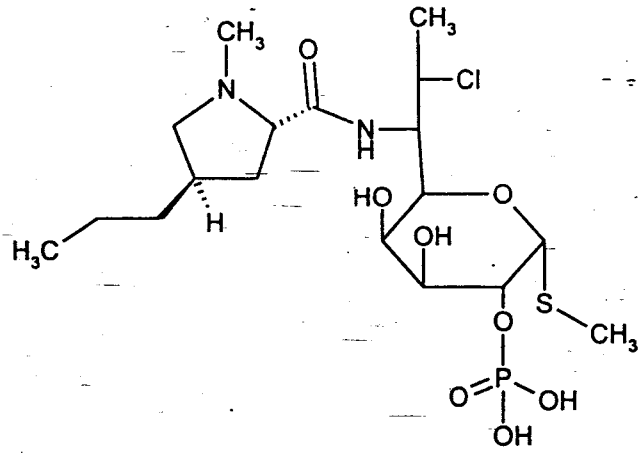
Clindamycin 1% and Benzoyl Peroxide 5% gel	**Dermik Laboratories, Inc.**
———— Topical Gel	**Collegeville, PA 19426**
Reviewer: A. Noory	**Submission Date:**
NDA 50-756	**April 9, 1998**

Review of an NDA

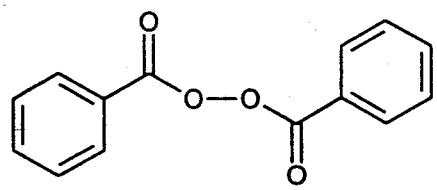
I. Background:

———— Topical Gel is a combination product containing 1% clindamycin phosphate and 5% benzoyl peroxide. Clindamycin phosphate is an antibacterial agent and benzoyl peroxide is also an antibacterial agent with mild keratolytic and desquamative activity. Both clindamycin and benzoyl peroxide are active against Propionibacterium acnes, a common microorganism thought to contribute to the pathogenesis of acne vulgaris.

Clindamycin phosphate is a water-soluble ester of the semi-synthetic antibiotic derived from the parent antibiotic lincomycin. The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-trans-4-propyl-L-2-pyrrolidinecarboxamido)-1-thio-L-threo-alpha-D-galacto-octopyranoside 2-(dihydrogen phosphate) with a molecular weight of 504.97 and the following structure.



Benzoyl peroxide ($C_{14}H_{10}O_4$) has a molecular weight of 242.23 with the following structure.



As part of the human pharmacokinetics and bioavailability portion of this NDA, the applicant has submitted the results of a pharmacokinetic study, two in vitro percutaneous absorption studies, and six literature-based studies.

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II. Recommendation:

In support of the pharmacokinetics and bioavailability portion of this NDA the sponsor submitted the result of a pharmacokinetic study and two in vitro percutaneous absorption studies. These studies failed to adequately describe the bioavailability of ——— Topical Gel. From the biopharmaceutics point of view the NDA 50-756 is not approvable.

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III. Overview of pharmacokinetics section:

The human pharmacokinetics and bioavailability section of this NDA consists of

1. A pharmacokinetic study, in which the applicant evaluated the systemic exposure and the bioavailability of clindamycin following the application of 1g of ——— Topical Gel.
2. An in vitro percutaneous absorption study, in which the applicant evaluated the permeation of clindamycin phosphate from ——— Topical Gel and Cleocin-T™ using human cadaver skin.
3. An in vitro percutaneous absorption study, in which the applicant evaluated the permeation of benzoyl peroxide in the presence and the absence of clindamycin from ——— Topical Gel using human cadaver skin.
4. Six literature-based studies (Not reviewed)

Formulation:

The proposed market formulation for ——— Topical Gel is shown on page 7 of the appendix. The pharmacist will have to compound ——— Topical Gel before dispensing. The product will be supplied to the pharmacist as benzoyl peroxide gel (19.7g), clindamycin powder (0.3g), and 5ml of purified water in separate containers.

Analytical:

[redacted]

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IV. Pharmacokinetic study (protocol DL-6021-9626):

The objective of this study was to assess the bioavailability of clindamycin and the systemic exposure to clindamycin following the topical application of 1gram of ——— Topical Gel. A single 1gram dose of ——— (1% clindamycin phosphate/5% benzoyl peroxide) topical gel was applied to a 225 cm^2 area on the face of sixteen (16) healthy subjects. No measurable levels of clindamycin phosphate, clindamycin sulfoxide, or clindamycin phosphate sulfoxide were detected in any of the plasma samples analyzed. The study summary is located on page 12 of the appendix.

One possible explanation for non-detectable level could be that benzoyl peroxide causes clindamycin to degrade on the surface of the skin. More importantly, the study was conducted using subjects with healthy skin. Healthy skin does not allow easy penetration of the drug substance into the dermis. Therefore this study cannot be used to assess the absorption of clindamycin after the application of ——— in a clinical setting.

V. In vitro percutaneous absorption (Study DL-6021-9402):

In this study the applicant compared the percutaneous penetration of 1% clindamycin as phosphate in ——— Topical Gel with that of Cleocin-T®Topical Gel. Four to six sections of human cadaver skin from four donors ——— were tested using ——— diffusion cells. The study consisted of four experiments. Experiment #1, (skin ———), was carried out for four days to assess the penetration and recovery of clindamycin. Experiment #2 was carried out using the skin of the other three donors. The receptor sample was collected at 12 hours and the surface exposure was evaluated at 48 hours. Experiment #3 (skin ——— was carried out similar to the experiment #2 except that the applied dose was twice the dose used in experiment #2. The result of these experiments is located in pages 13-16 of the appendix and a summary of the result is shown in the following table.

Clindamycin: In Vitro percutaneous penetration; Mean (SD)					
	Product	Dose (µg)	Total Penetration (µg)	Total Recovery	% of dose Recovered
Exp.1 1 donor	———	113	2.82	73.15	64.73
	Cleocin-T	99	0	110.99	112.11
Exp.2 3 donors	———	113	0.58 (0.15)	75.41 (6.45)	66.74 (5.71)
	Cleocin-T	99	0.457 (0.79)	99.44 (4.38)	100.44 (4.35)
Exp.3 1 donor	———	226	0	83.47	73.86
	Cleocin-T	198	0	112.12	113.53

Experiment #4 (skin ———) was designed to assess the degradation of clindamycin at 3, 7, 20.5, and 48 hours when the surfaces were washed and the wash was analyzed. The result of this study shows a loss of clindamycin after 3 hours. Between 3 and 7 hours, 16% has been lost and by 20.5 hours, 24.5% of the Clindamycin phosphate is no longer detectable.

The result of this study shows a degradation of clindamycin phosphate in the presence of benzoyl peroxide on the surface of the skin. Additionally the results of these experiments show that very little clindamycin penetrates the skin (0.5% in experiment #2). The utility of these informations is rather limited due to both the small number of donors and number of samples, and the fact that cadaver skin is metabolically inactive. The fact that healthy skin may further degrade clindamycin makes these estimates of clindamycin degradation lower limits only.

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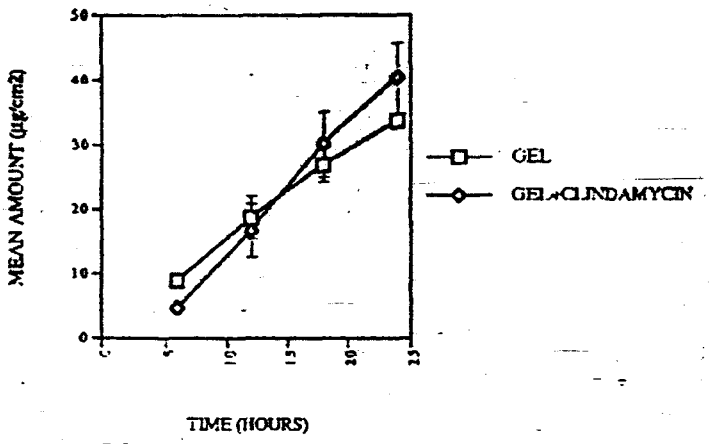
VI. In vitro percutaneous absorption (Study DL-6021-9706):

The objective of this study was to compare the in vitro percutaneous absorption of benzoyl peroxide in Dermik's combination product (1% clindamycin/5% benzoyl peroxide) with 5% benzoyl peroxide gel to determine if clindamycin effected the absorption of benzoyl peroxide. Human cadaver skin from a single donor was sectioned, into five specimens and mounted into ——— diffusion cells. 6 mgs of ^{14}C-labeled benzoyl peroxide gel formulations was then applied to the skin. A ——— ——————— was used to analyze/count each sample for 5 minutes every 6 hours up to 24 hours. The appearance of benzoyl peroxide in the receptor is shown in the following figure and the data are located on page 17 of the appendix.



The table below shows the percent of benzoyl peroxide absorbed from the two gels.

Percent Benzoyl Peroxide Absorbed			
Formulation	Amount Applied	Amount Absorbed	Percent Absorbed
Benzoyl peroxide	203 µg	45.1 µg	22.2%
Benzoyl peroxide/Clindamycin	194 µg	50.9 µg	26.2%

These results indicate that the absorption of benzoyl peroxide was 18% higher in the presence of clindamycin. Because only the skin of one donor was used in this study, no conclusion can be made regarding its outcome.

VII. Comment:

The use of healthy subjects in a pharmacokinetic study (DL-6021-9626) is not appropriate. The study should be conducted in a clinical setting. Healthy skin does not allow easy penetration of most drug substances into the dermis. This study, therefore, cannot be used to assess the absorption of clindamycin after the application of Clinoxin® Topical Gel.

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VIII. Deficiency: (to be forwarded to the applicant)

The pharmacokinetic study (DL-6021-9626) was not a representative of the actual use of this product, ie, long term use by patients with acne vulgaris. The applicant should have designed the study so that it would include the following.

1. Patients with acne vulgaris on the skin of the face as well as on other appropriate area of the body.
2. Apply the maximum recommended dose over the diseased skin (face and other area) consistent with their proposed labeling.
3. A multiple dose pharmacokinetic study that would resemble a clinical setting in terms of dosing frequency and usage.

[/S/ 2/1/99]

Assadollah Noory
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm.D [/S/ 2/1/99]

CC: NDA 50-756,
HFD-540/DIV. File
HFD-540/Prj. Mjr./KWhite
HFD-880 (Noory)
HFD-880 (Bashaw)
HFD-880 (Lazor)
(CDR. Attn. B. Murphy)
HFD-344 (Viswanathan)

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Appendix

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Drug Product - Quantitative Composition

Ingredients	Quantity/Gram
Clindamycin Phosphate, USP (Active)	— mg
Hydrous Benzoyl Peroxide, USP (Active)	— mg
Carbomer — NF	———
Sodium Hydroxide, NF	———
Dioctyl Sodium Sulfsuccinate, ——	———
Purified Water	———

HOW SUPPLIED AND COMPOUNDING INSTRUCTIONS

Size (Net Weight)	NDC 0066-	Benzoyl Peroxide Gel	Active Clindamycin Powder (In plastic vial)	Purified Water To Be Added
25 grams	0494-25	19.7g	0.3g	5 mL

Prior to dispensing, tap vial until powder flows freely. Add purified water to vial (to the mark) and immediately shake to completely dissolve clindamycin. If needed, add additional purified water to bring level up to the mark. Add this solution to gel and stir until homogenous in appearance (1 to 1½ minutes). ——— **Topical Gel** should then be stored under refrigeration. Do not freeze. Place a — month expiration date on the label. Place a STORE REFRIGERATED sticker onto the jar.

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NDA # 50-756 Submission Date: April 9, 1998 Volume: 1.14

Study Type: Pharmacokinetics Study # DL-6021-9626

Study Title: Single Dose Pharmacokinetics of Topical Clindamycin 1% and Benzoyl Peroxide 5% Gel

Clinical Investigator: [redacted] Analytical Investigator: [redacted]

Site: [redacted] Site: [redacted]

Study Objective: To assess the systemic exposure to and the bioavailability of clindamycin following a 1g application of topical 1% clindamycin/5% benzoyl peroxide.

Study Design:

Single Dose: X	Multiple Dose:	Randomized:	Washout Period:
Cross-Over:	Parallel:	Other Design:	Single Center:
Fasted: _	Post Dosing:		
Food Study:	Food Type:		

Study Subjects: Sixteen subjects were enrolled in this study.

Gender	No. of Subj.	Mean Age (yr)	Range (yr)	Mean Weight (kg)	Range (kg)
Female	12	36.6	19 - 64	65.6	48.2 – 83.2
Male	4	39.7	23 - 71	80.2	71.8 – 87.7

Study Drug: 0.36 g of clindamycin phosphate powder was dissolved in 5ml of distilled water and the solution was added to a jar of 5% benzoyl peroxide gel, and mixed to a homogeneous appearance.

Drug Product: One gram of [redacted] Topical Gel contains the active ingredients shown in table below.

Active ingredients	Amount	Dosage Form	Packing	Batch #
Clindamycin Phosphate	[redacted] mg	Topical Gel	Mixed by	PST115
Benzoyl Peroxide	[redacted] mg		pharmacist	PST211

Sampling Times

Plasma: Blood samples were collected at 0, 1, 2, 4, 8, 12, and 24 hours after dose administration.

Analytical

[redacted]

Results:

None of the plasma samples were quantifiable.

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Clindamycin Study: Overall Summary

Cleocin-T Product Dose: 99 ug

Sample Skin:						Mean	SE
Receptor 1						0.022	0.022
Receptor 2						0.015	0.015
Receptor 3						0.004	0.004
Receptor 4						0.000	0.000
Total Penetration						0.27	0.35
Epidermis						0.05	0.00
Dermis						0.01	0.00
Surface Wash						04.01	2.02
Total Recovery:						104.34	1.93
% of Applied dose:						105.40	1.95
# Sections tested:	5	4	4	6	4		

Dermik Product Dose: 113 ug

Sample Skin:						Mean	SE
Receptor 1						0.035	0.016
Receptor 2						0.004	0.003
Receptor 3						0.007	0.004
Receptor 4						0.000	0.000
Total Penetration						0.91	0.07
Epidermis						0.04	0.00
Dermis						0.13	0.09
Surface Wash						75.49	3.03
Total Recovery:						76.57	2.89
% of Applied dose:						67.76	2.55
# Sections tested:	5	5	4	5	4		

Table 1: Final summary data for the percutaneous absorption and mass balance of Clindamycin phosphate from Cleocin-T and the Dermik formulation. Receptors are as $\mu g/hr/cm^2$; Total penetration, epidermis, dermis, surface wash and total recovery are as µg. Skin —— data corrected for dose applied.

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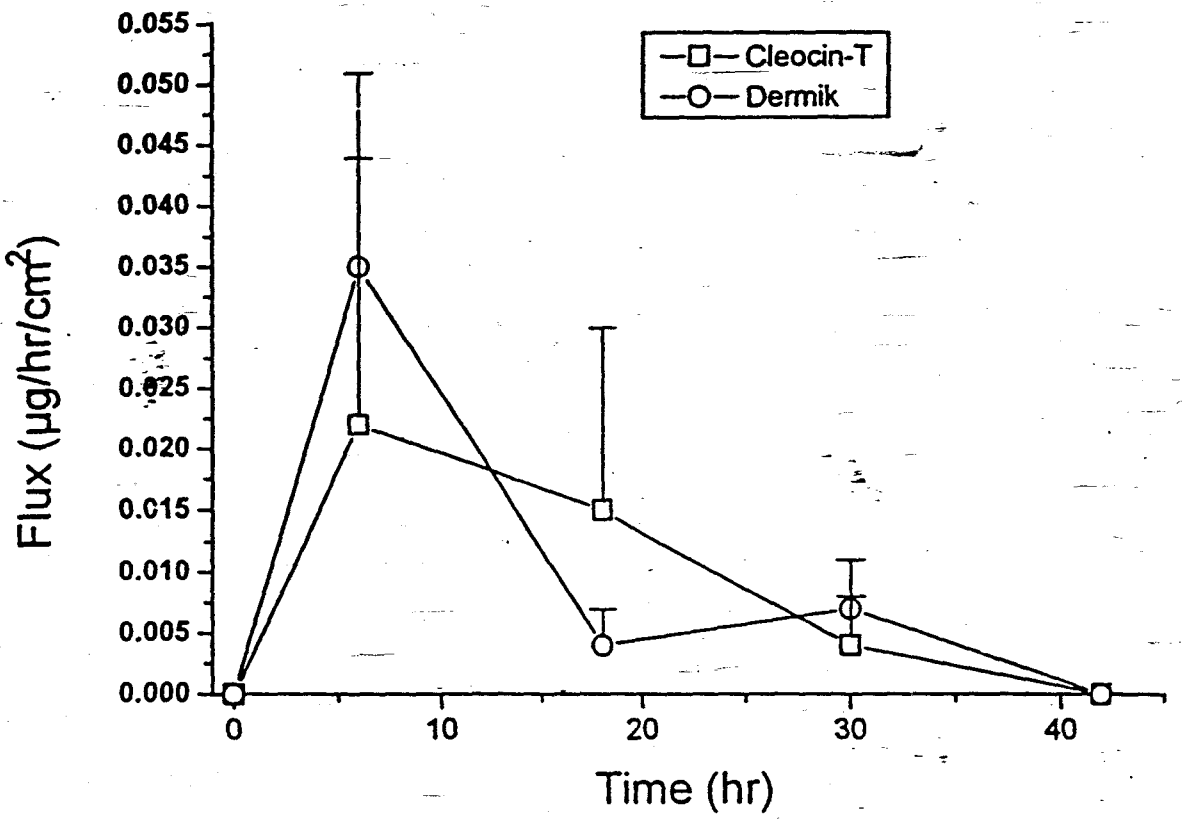

Figure 1: Flux profile of the percutaneous absorption of Clindamycin phosphate.
Data are mean ± SE as µg/hr/cm^2.

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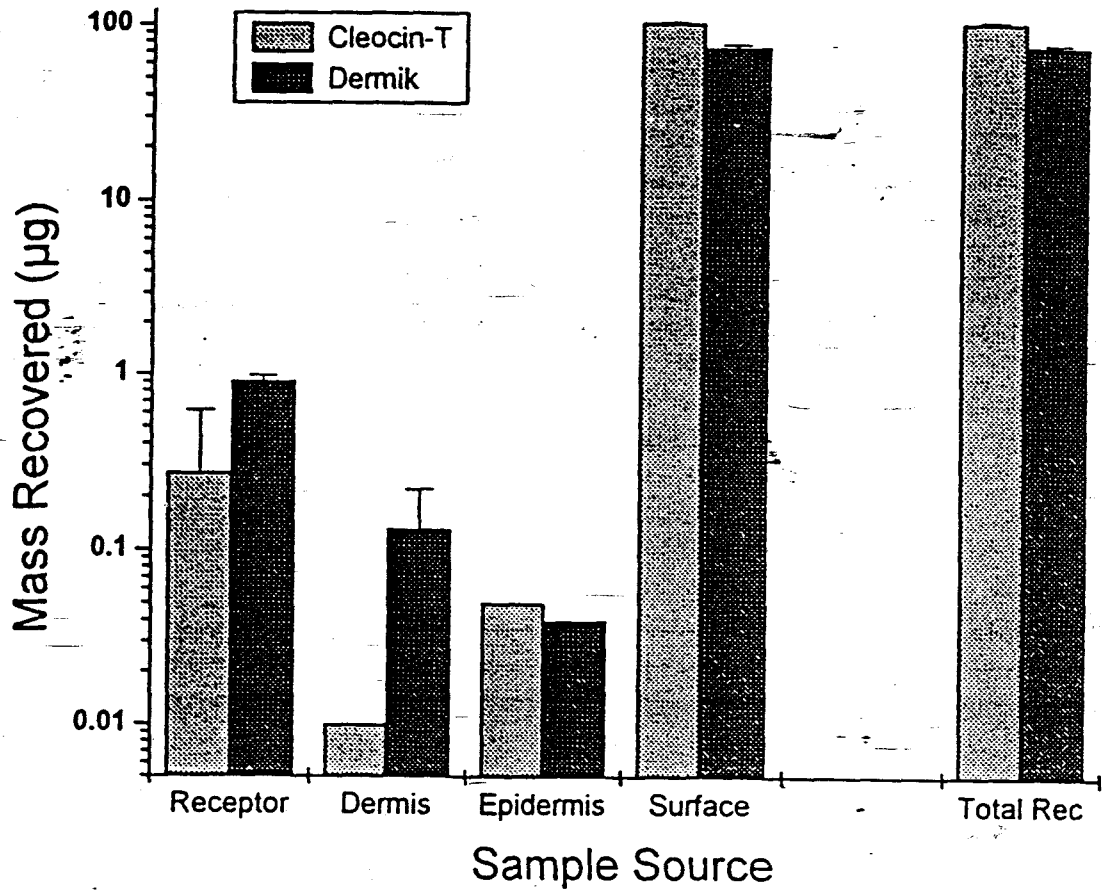

Figure 2: Recovery of Clindamycin phosphate in the various compartments analyzed using the finite dose human cadaver in vitro model. Data are mean ± SE.

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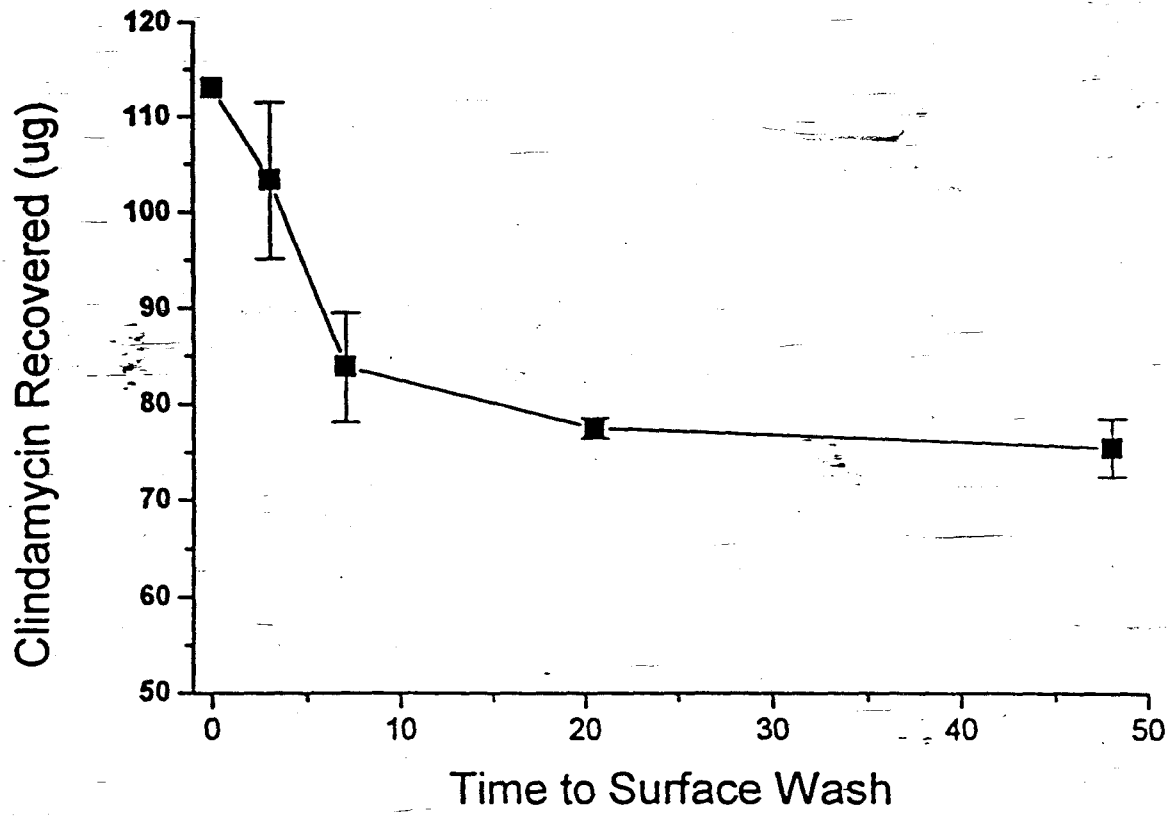

Figure 4: Recovery of Clindamycin phosphate from the skin surface across time.
Data are mean ± SD (n=2 for 3, 7 and 21.5 hr data points, n=5 for 48 hr data point)
Zero data point assumed 100% vehicle concentration determined as 113 ug.

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BENZOYL PEROXIDE GEL TIME (HOURS)	CELL 1 CUM (µg/cm2)	CELL 2 CUM (µg/cm2)	CELL 3 CUM (µg/cm2)	CELL 4 CUM (µg/cm2)	CELL 5 CUM (µg/cm2)	MEAN	STD ERROR MEAN	STDEV
6						8.580	1.639	3.664
12						18.461	3.402	7.607
18						26.657	2.615	5.846
24						33.285	1.509	3.374
Total of receptor						33.285	1.509	3.374
% RECEPTOR/APPLIED						10.431	0.343	0.766
AT 24 HOURS	CELL-1(µg)	CELL-2(µg)	CELL-3(µg)	CELL-4(µg)	CELL-5(µg)			
WASH								
SC						5.101	0.777	1.738
VIABLE SKIN						18.810	2.812	6.289
RECEPTOR						21.169	0.960	2.146
TOTAL AMOUNT								
APPLIED AMOUNT								
% RECOVERY								
TOTAL ABSORBED						45.081		
% SKIN/TOTAL ABSORBED						53.041		

BENZ. PER./CLINDA. GEL TIME (HOURS)	CELL 1 CUM (µg/cm2)	CELL 2 CUM (µg/cm2)	CELL 3 CUM (µg/cm2)	CELL 4 CUM (µg/cm2)	CELL 5 CUM (µg/cm2)	MEAN	STD ERROR MEAN	STDEV
6						4.413	1.480	3.309
12						16.454	4.159	9.300
18						29.821	5.048	11.288
24						40.022	5.514	12.329
Total of receptor						40.022	5.514	12.329
% RECEPTOR/APPLIED						13.085	1.611	3.602
AT 24 HOURS	CELL-1(µg)	CELL-2(µg)	CELL-3(µg)	CELL-4(µg)	CELL-5(µg)			
WASH								
SC						5.459	0.163	1.035
VIABLE SKIN						20.027	1.474	3.295
RECEPTOR						25.454	3.507	7.841
TOTAL AMOUNT								
APPLIED AMOUNT								
% RECOVERY								
TOTAL ABSORBED						50.941		
% SKIN/TOTAL ABSORBED						50.032		