CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

64160

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 64-160 SPONSOR : Altana, Inc.

DRUG AND DOSAGE FORM : **Clindamycin Phosphate Gel**

STRENGTH(S) : 1%

TYPES OF STUDIES : In-vivo Bioequivalence with clinical endpoints

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : A randomized , double blind, 12 week, multicenter, placebo-controlled clinical trial to determine the bioequivalence of clindamycin phosphate gel, 1% formulation of Altana's product vs Pharmacia & Upjohn's Cleocin T Gel, 1%, in the treatment of moderately severe Acne Vulgaris. Altana's product was found to be bioequivalent to the reference product.

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / (NO)	Inspection status:	Inspection results:
First Generic ____	Inspection requested: (date)	Original submission was before April 1, 1999.
New facility ____	Inspection completed: (date)	
For cause ____		
Other ____		

PRIMARY REVIEWER : Mary Fanning, MD BRANCH : Associate Director for Medical Affairs

INITIAL : /S/ DATE : 1/5/00

TEAM LEADER : (NAME) BRANCH :

INITIAL : /S/ DATE : 1/21/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : /S/ DATE : 1/24/00

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 64-160 APPLICANT: Fougera (Altana, Inc.)

DRUG PRODUCT: Clindamycin Phosphate Gel 1%

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

1st

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JUN 14 1996

Clindamycin Phosphate Gel, USP, 1%
ANDA # 64-160
Reviewer: Man M.Kochhar

Fougera
Melville, N.Y.
Submission Date:
February 6, 1996

REVIEW OF A WAIVER REQUEST

The company has requested a waiver of the bioequivalence requirement for their clindamycin phosphate gel, USP, 1% under the provision of 21 CFR 320.22 (b)(3). The product is intended for topical use only.

The composition of the product is as follows:

Ingredients	Fougera	Upjohn
Clindamycin (from Clindamycin Phosphate)	10 mg/g (1%)	10 mg/g (1%)
Carbomer 934P		
Propylene Glycol		
Polyethylene Glycol 400		
Methylparaben		
Sodium Hydroxide		
Purified Water, USP		

Comments:

1. The indications for use and labeling of the test product are identical to those of the reference product Cleocin T topical Gel manufactured by Upjohn.

2. The quantities of active and inactive ingredients in both formulations are same.

3. Clindamycin phosphate topical gel USP, 1% is a post-1962 semisolid topical drug product which requires an in vivo bioequivalence study with a clinical end point.

4. The OGD recommends that a protocol for the clinical bioequivalence study should be submitted to the Division of Bioequivalence for review before any studies are initiated.

Recommendations:

1. The Division of Bioequivalence does not agrees that the information submitted by Fougera, A Division of Altana Inc. demonstrates that Clindamycin Phosphate Gel, USP, 1% falls under 21 CFR 320.22 (b)(3) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study

requirements for Clindamycin Phosphate 1% topical gel can not be granted for the reasons cited under comments 3 and 4.

The firm should be informed of the recommendation.

/S/

Man M. Kochhar, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/

Concur: /S/ Date: 6/14/96
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA # 64-160 original, HFD-630, HFD-600 (Hare), HFD-658 (Mhatre, Kochhar), Drug File, Division File

(3) THE DRUG PRODUCT:

(i) IS A SOLUTION FOR APPLICATION TO THE SKIN, AN ORAL SOLUTION, ELIXIR, SYRUP, TINCTURE, OR SIMILAR **OTHER SOLUBILIZED FORM**;

(ii) CONTAINS AN ACTIVE DRUG INGREDIENT IN THE SAME CONCENTRATION AND DOSAGE FORM AS A DRUG PRODUCT THAT IS THE SUBJECT OF AN APPROVED FULL NEW DRUG APPLICATION; AND

(iii) CONTAINS NO INACTIVE INGREDIENT OR OTHER CHANGE IN FORMULATION FROM THE DRUG PRODUCT THAT IS THE SUBJECT OF THE APPROVED FULL NEW DRUG APPLICATION THAT MAY SIGNIFICANTLY AFFECT ABSORPTION OF THE ACTIVE DRUG INGREDIENT OR ACTIVE MOIETY.

CLINDAMYCIN PHOSPHATE

CREAM; VAGINAL		
CLEOCIN		
+ UPJOHN	EQ 2% BASE	N50680 001 AUG 11, 1992
GEL; TOPICAL		
CLEOCIN T		
+ UPJOHN	EQ 1% BASE	N50615 001 JAN 07, 1987

ERYTHROMYCIN

GEL; TOPICAL

	EMGEL			
AT	GLAXO WELLCOME	2%		N63107 001 AUG 23, 1991
	ERYGEL			
AT	+ ALLERGAN HERBERT	2%		N50617 001 OCT 21, 1987
	ERYTHROMYCIN			
AT	STIEFEL	2%		N63211 001 JAN 29, 1993

Clindamycin Phosphate Gel USP, 1%

1. Clindamycin Phosphate (Clindamycin	1.1882% 1%)
2. Carbomer 934P	%
3. Allantoin	%
4. Polyethylene Glycol 400	%
5. Propylene Glycol	%
6. Methylparaben	%
7. Sodium Hydroxide	
8. Purified Water	q.s.

Clindamycin Phosphate Gel USP, 1%

1.	Clindamycin Phosphate (Clindamycin	1.1882% 1%)

Multiply by the ratio of the molecular weights

1% x 504.97 / 424.98 = 1.1882%

Adjust based on "as is" potency of the clindamycin phosphate

Clindamycin Phosphate Gel USP, 1%

2. Carbomer 934P **%**

Level chosen by matching the rheology of Cleocin T

pH at the specification midpoint

Clindamycin Phosphate Gel USP, 1%

3. Allantoin %

% referenced in FDA's Summary Basis of Approval

with evaporative light-scattering detector: %

detection at %

Clindamycin Phosphate Gel USP, 1%

4. Polyethylene Glycol 400 **%**

with evaporative light-scattering detector: **%**

Clindamycin Phosphate Gel USP, 1%

5. Propylene Glycol %

using a differential refractometer as detector: %

chromatography: %

Clindamycin Phosphate Gel USP, 1%

6. Methylparaben **%**

detector at **:** **%**

(Upjohn claims 0.3% in Cleocin T Lotion)

Clindamycin Phosphate Gel USP, 1%

7. Sodium Hydroxide

%)

Midpoint of USP specification of ..

Cleocin T mean pH of 5.7

Manufacturing instructions require .. ...

Clindamycin Phosphate Gel USP, 1%

8. Purified Water	**q.s.**

Weight may vary slightly based on the actual amounts of clindamycin phosphate (adjusted for potency) and sodium hydroxide

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pages of trade

secret and/or

confidential

commercial

information

Manufacturing Process

Clindamycin Phosphate Gel USP, 1%

Release Rates
micrograms per centimeter squared versus the square root of minutes

Altana

111.411
128.130
128.157
116.958
135.115
122.304

Upjohn

124.715
135.438
120.097
137.695
131.212
126.650

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secret and/or

confidential

commercial

information

Clindamycin Phosphate Gel USP, 1%

Using a nonparametric statistical test, the 90% confidence interval for the ratio of the median *in vitro* release rate of the Altana gel divided by the median *in vitro* release rate of the Upjohn gel is:

89.14% to 102.74%

This range is easily encompassed by the 75.00% to 133.33% range suggested for demonstrating the equivalence of two semisolids.

Polymer-Based Gels: Drug Release, Topical Delivery and Bioequivalence

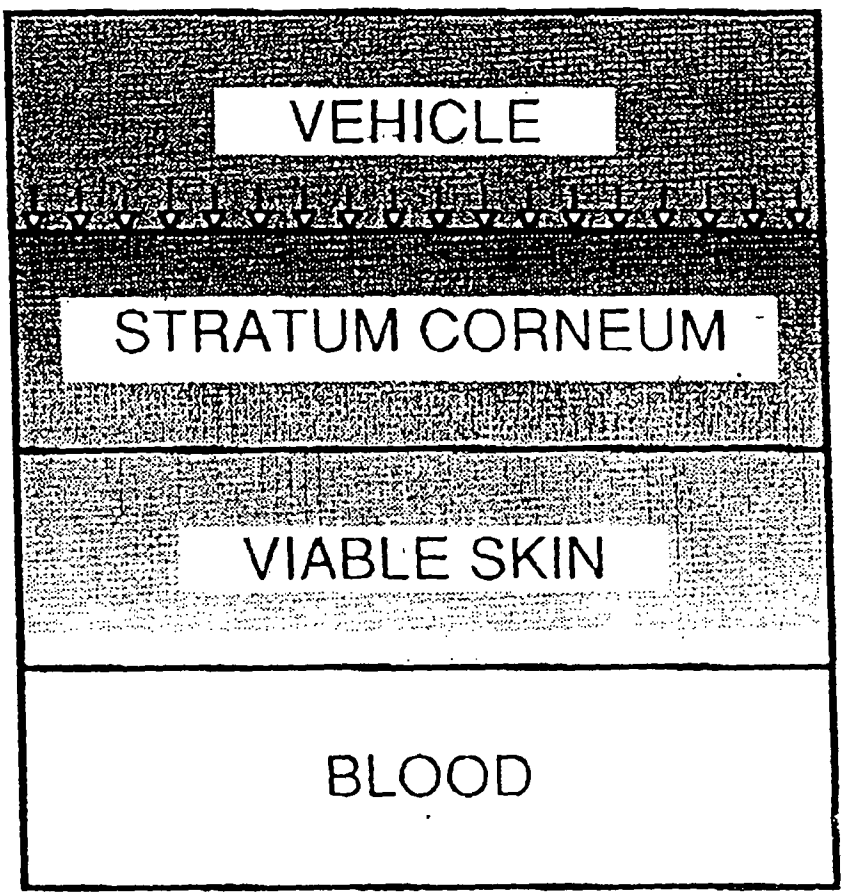
Joel L. Zatz, Ph.D.

Rutgers University

"The main factors in the physicochemical relationship of the penetrant to the vehicle appear to be the solubility of the penetrant in the vehicle or a constituent of the vehicle, the rate of diffusion of the penetrant within the vehicle, the rate of release of the penetrant from the vehicle, and the possible release of the penetrant in solubilized form together with a constituent of the vehicle."

from B. Idson, "Percutaneous Absorption", *J. Pharm. Sci.*, 64, 901 (1975)

SKIN PERMEATION SCHEMATIC



GELS

Definition: Semisolid based on 3-dimensional network of molecules or particles; frequently high liquid content.

GEL-FORMING AGENTS

In water: Gums (tragacanth, pectin)
Montmorillonite clays (5% Veegum)
Nonionic surfactant (20-40% Brij)
Cellulose derivatives (CMC + Al salts)
Sodium alginate + Ca salts
Carbomer (Carbopol®; 1-3%)

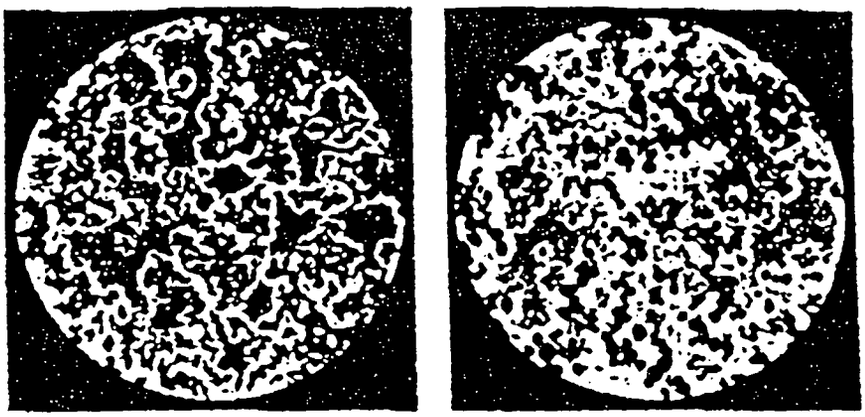
$$-(CH_2\text{-}CH)_x- \;+\; BASE \;\rightarrow\; -(CH_2\text{-}CH)_x-$$
$$\quad\;\; | \qquad\qquad\qquad\qquad\qquad\quad |$$
$$\quad COOH \qquad\qquad\qquad\qquad\quad COO^-$$

In semipolar liquids:
Hydroxypropylcellulose (Klucel)
Clay derivatives (Bentones)
Microcrystalline silica

In nonpolar liquids:
Aluminum stearate
Long chain alcohols, waxes
Polyethylene and polyethylene copolymers

AEROSIL MOX 80

AEROSIL OX 50



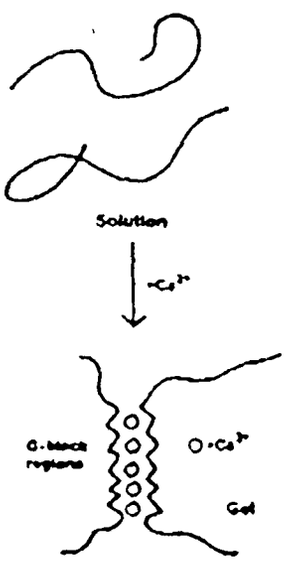
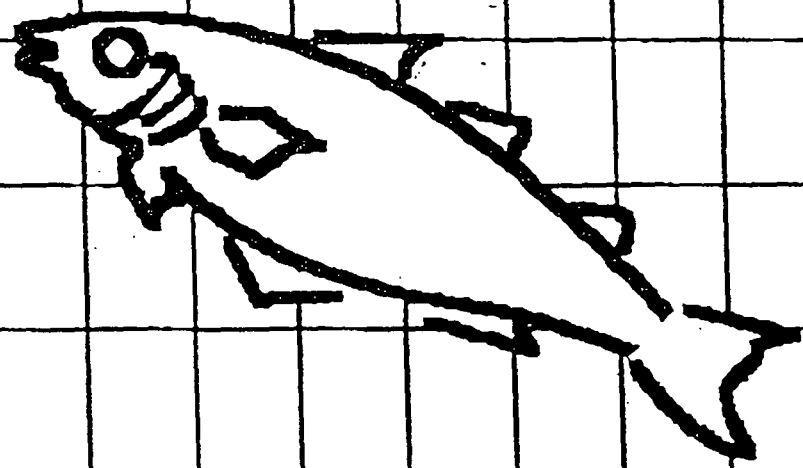
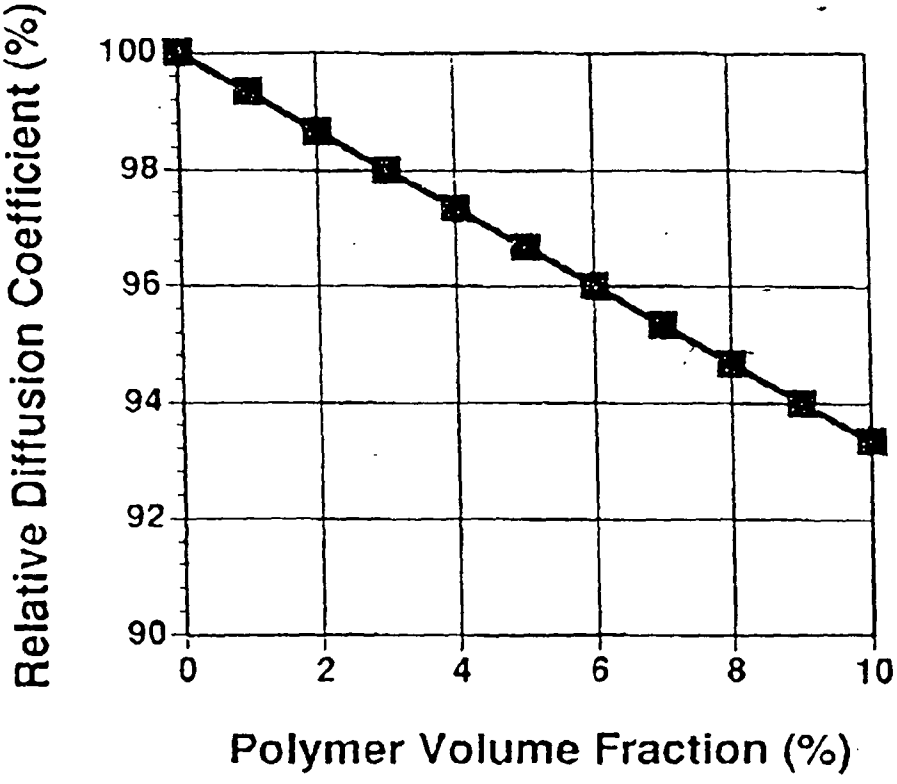


Figure 3. Egg box model for alginate gelation



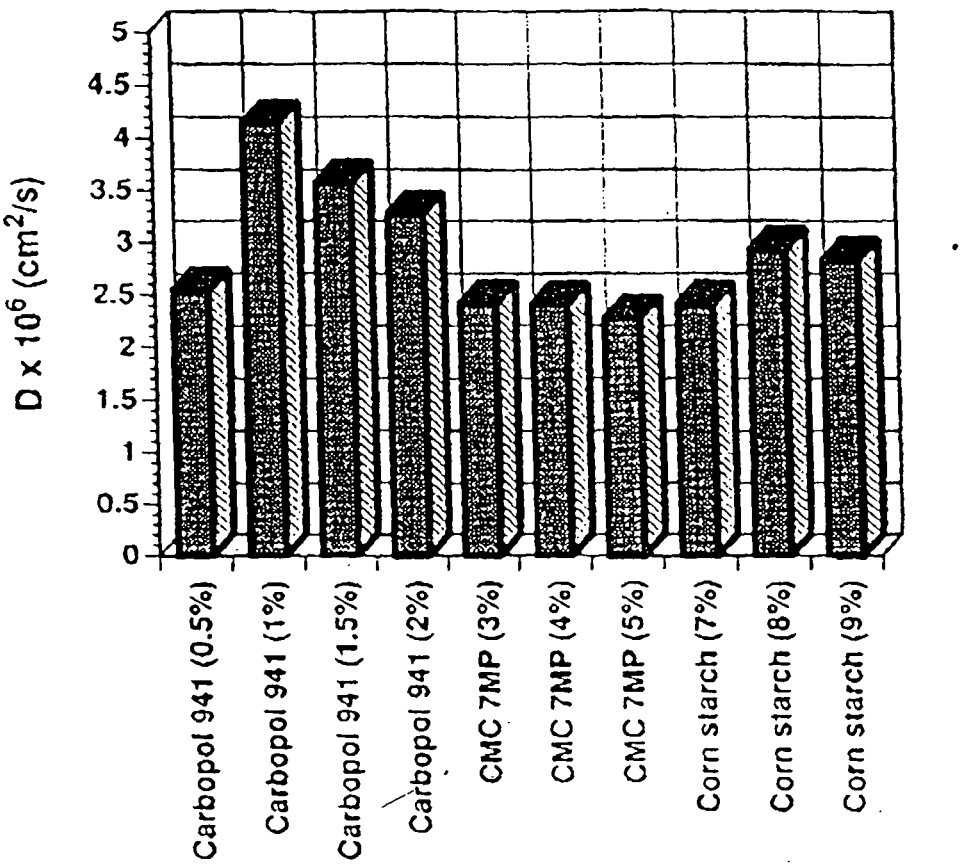
Diffusion in Polymer-Based Gels

[References: M. Laufer, *Biophys. J.*, 1, 205 (1961); G. L. Flynn et al., *J. Pharm. Sci.*, 63, 479 (1974)]



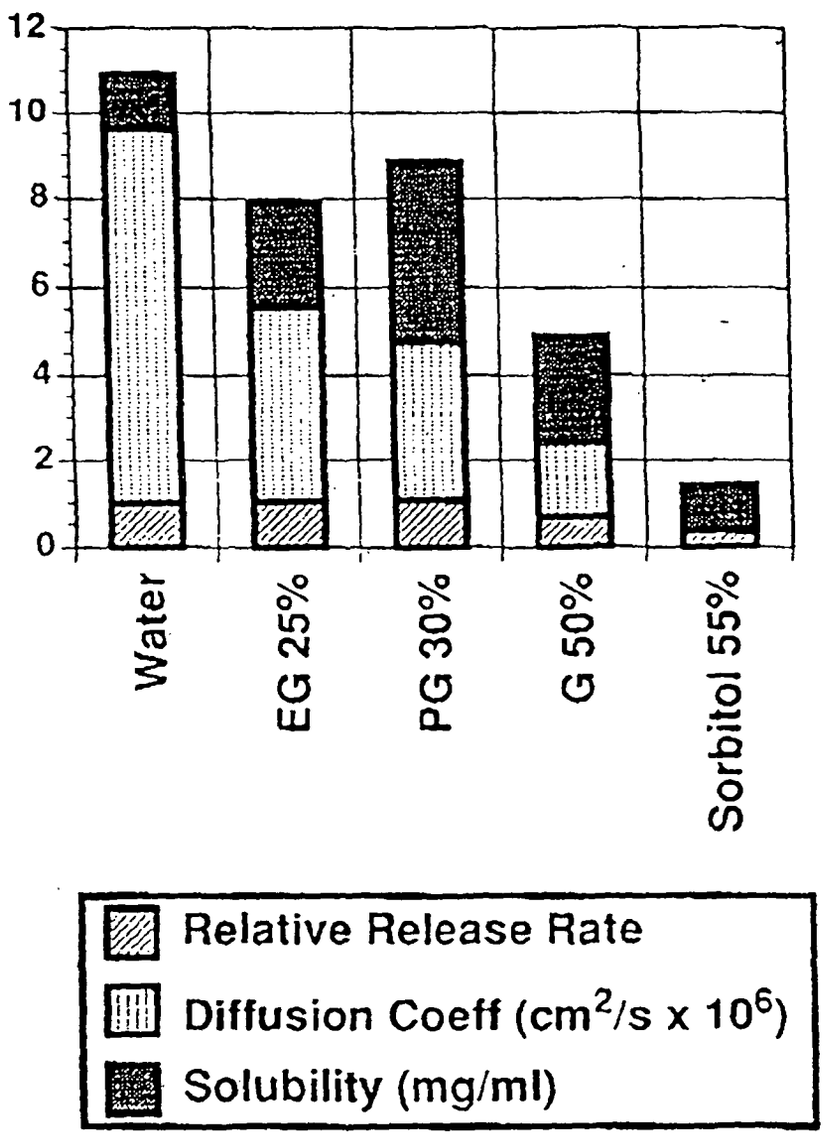
Resorcinol Release from 5% Aqueous Gels

[Data from Spang and Brunner, *J. Pharm. Pharmacol.*, 28, 23 (1976)]



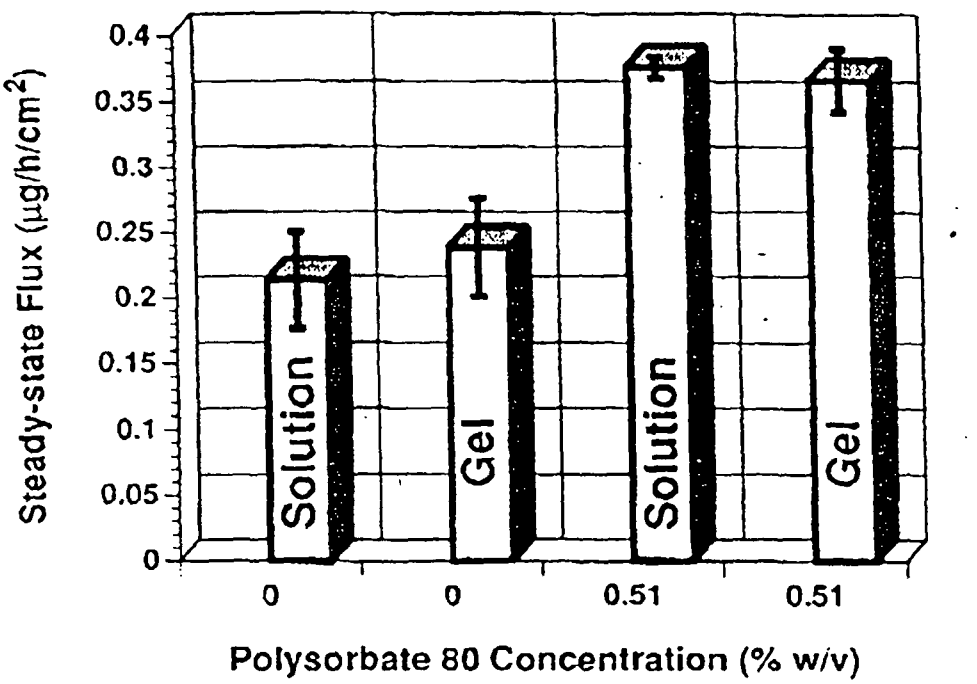
Benzocaine Release from Aqueous Gel Suspensions Containing 1% Carbopol 934

[Data from Di Colo et al., *J. Pharm. Sci.*, 69, 387 (1980)]

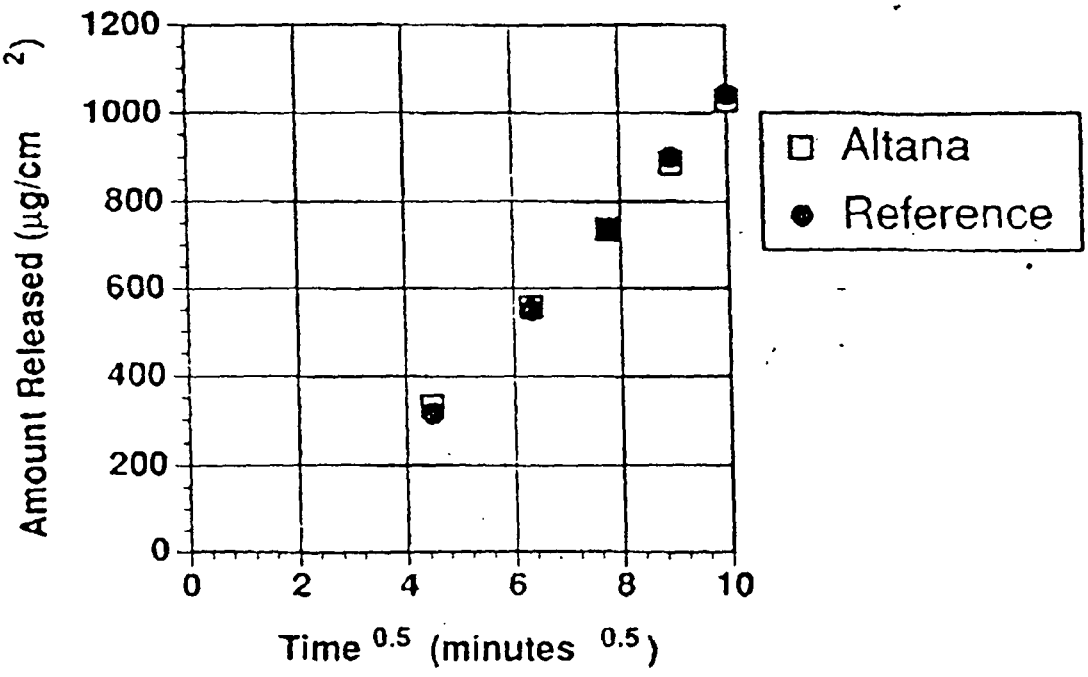


Hydrocortisone Flux from 0.2% Solutions in 40% Isopropanol/Water. Gellant: 1% HEC

[Data from Shahi and Zatz, *J. Pharm. Sci.*, 67, 789 (1978)]



Mean Clindamycin Release from Altana and Reference Gels (n=6)



Slopes for mean data:

Altana: **126 µg/cm2/√min**

Reference: **132 µg/cm2/√min**

CONCLUSIONS

1. Simple one-phase gels are highly porous, liquid-filled structures.
2. In the absence of specific binding, the diffusion coefficient of a dissolved drug in a simple gel is essentially the same as in the solution used to form the gel.
3. Release and skin penetration depend on solvent composition.
4. Skin penetration flux from solutions and comparable simple gels, absent specific binding, are identical.
5. There is no difference in in-vitro release from the Altana Clindamycin Phosphate gel and the reference product.

RECOMMENDATION

Two Topical Products should be Considered Bioequivalent if:

1. Test product and reference are Q and Q.
2. Both products are simple one-phase gels containing ≤ 5% gellant.
3. The drug is totally dissolved in both products.

Altana's Clindamycin Phosphate gel satisfies these requirements and shows identical release to the reference product.

Selected Recent Works on Skin Delivery, Drug Release and Gels by J. L. Zatz

J. L. Zatz and G. P. Kushla, "Gels", in *Pharmaceutical Dosage Forms; Disperse Systems*, H. Lieberman, M. Rieger and G. Banker, Eds., Dekker, NY, 1989, Vol. 2, pp. 495-510.

J. N. Twist and J. L. Zatz, "Interaction of Vehicles with Model Skin Membranes in the Permeation Process", *Percutaneous Absorption*, Second Edition, R. Bronaugh and H. Maibach, Eds., Dekker, NY, 1989, pp. 147-173.

J. L. Zatz, "Assessment of Vehicle Factors Influencing Percutaneous Absorption," *In Vitro Percutaneous Absorption: Principles, Fundamentals and Applications*, R. Bronaugh and H. Maibach, Eds., CRC Press, Boca Raton, 1991, pp. 51-66.

J. L. Zatz (Editor and contributor), *Skin Permeation*, Allured, 1993.

H. M. Fares and J. L. Zatz, "Measurement of Drug Release from Topical Gels Using Two Types of Apparatus," *Pharm. Tech.*, 19(1), 52-58 (1995).

J. L. Zatz, "The Formulation of Dermatologic Vehicles," *Cutis*, 55 (4S), 17-27 (1995).

J. L. Zatz, "Drug Release from Semisolids: Effect of Membrane Permeability on Sensitivity to Product Parameters," *Pharm. Res.*, 12, 787-789 (1995).

J. L. Zatz and G. P. Kushla, "Gels", in *Pharmaceutical Dosage Forms; Disperse Systems*, 2nd Ed., H. Lieberman, M. Rieger and G. Banker, Eds., Dekker, NY, 1996, Vol. 2, pp. 399-421.

J. L. Zatz, J. Varsano and V. P. Shah, "In Vitro Release of Betamethasone Dipropionate from Petrolatum-Based Ointments", *Pharm. Dev. Technol.*, in press.

J. D. Segers, J. L. Zatz and V. P. Shah, "In Vitro Release of Phenol from Ointment Formulations", *Pharm. Tech.*, in press.

Short course, Center for Professional Advancement, Presented twice a year since 1985. "Skin Product Development"

Lecture for FDA inspectors, University of Maryland, May 1993. "Semisolids and Topical Delivery"

Workshop on Scale-up of Liquid and Semisolid Disperse Systems, American Association Of Pharmaceutical Scientists, FDA and USP, May, 1993. "Overview-Creams/Ointments/Gels and Associated Issues of Scale-up"

CTFA Annual Scientific Meeting, October 1993. "Principles of Release Measurements on Topical Products"

Conference on "Insights into Dermatologic Drug Development. Linking Bioavailability, Bioequivalency and Therapy", October, 1995. "Predicting Formulation Activity"

Conference on Advances in the Biology of the Skin: Pharmacology and Toxicology, June 1996. "Formulation and Topical Drug Delivery"

AAPS Workshop on Bioequivalence. September, 1996. "In Vitro Release Methodology and its Use"

SUMMARY

BACKGROUND

On June 1996, we sent a letter to the company to submit a biostudy for their Clindamycin Phosphate Gel USP, 1%.

The sponsor has requested a meeting to discuss their submission on Clindamycin Phosphate Gel USP, 1%. They feel a waiver should be granted based upon CFR 320.22 (b)(3).

COMMENT

The request for a meeting is based upon the scientific facts that clindamycin phosphate gel USP, 1% is a single-phase gel in which the drug is completely dissolved and with a polymer content of less than 1%. This gel is Q and Q with respect to reference product and meets the other requirements for equivalent drug diffusion characteristics. Therefore, both test and reference products should be considered bioequivalent as simple solutions.

The sponsor has submitted documentations to show that the polymer does not interfere with the absorption of the drug from the skin. Gel may be defined as semisolids based on a network of cross-linked polymer molecules or insoluble molecules. One-phase gels are relatively simple preparations containing essentially a dissolved drug, a solvent system and a polymeric gelling agent.

The macroscopic viscosity of simple One-phase gel systems may be very high, reaching into the thousands of centipoise, largly because the crosslinked polymer molecules resist distortion and impede flow. However, the microscopin viscosity, which is a function of properties of solution within the gel, is unaffected. The diffusional properties within such a gel are thus quite similar to a solution lacking the gelling polymer. In other words, transport of dissolved drug molecules is largly unaffected by polymers molecules, because they occupy such a small fraction of the total volume of the system

The sponsor has provided experimental data to prove their point which are attached to this review.

Single-phase gels are one step removed from simple solutions in complexity. These gels are essentially solutions to which a gelling polymer has been added. The polymer provides a structural framework that makes the system behave as a semisolid. At the same time, the drug's diffusional properties depend on the medium and are essentially independent of the polymer, provided that there is no drug binding. However, even this restriction is of no consequence when comparing two gels containing the polymer at the same concentration.

I feel that a meeting should be granted as suggested by the company.

Kochhar

Figure 3. Effect of polymer concentration on drug diffusion

Diffusion in Polymer-Based Gels

[References: M. Laufer, *Biophys. J.*, 1, 205 (1961); G. L. Flynn et al., *J. Pharm. Sci.*, 63, 479 (1974)]

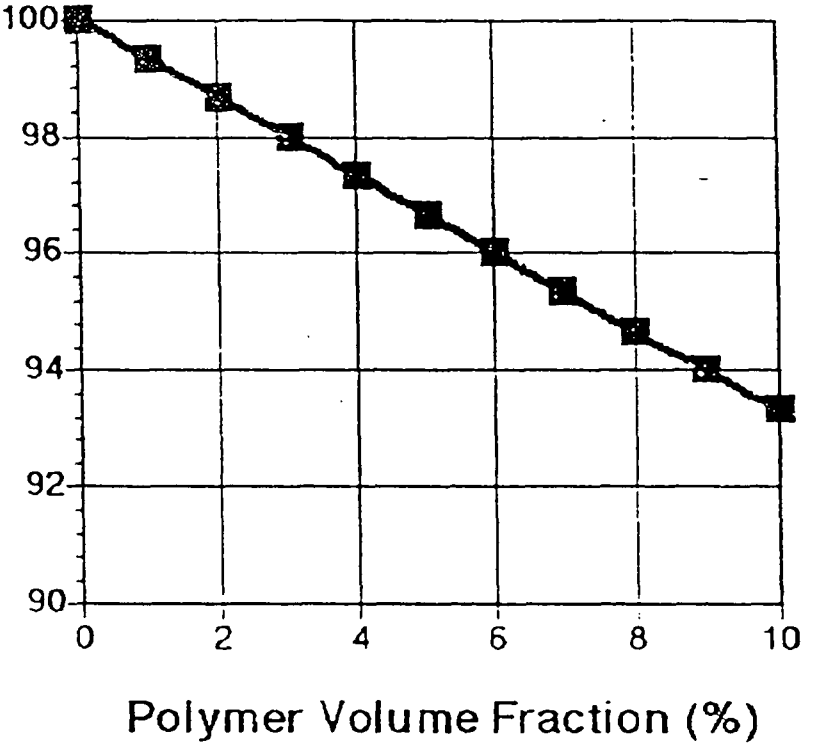


Figure 4. Resorcinol diffusion in gels containing various polymers

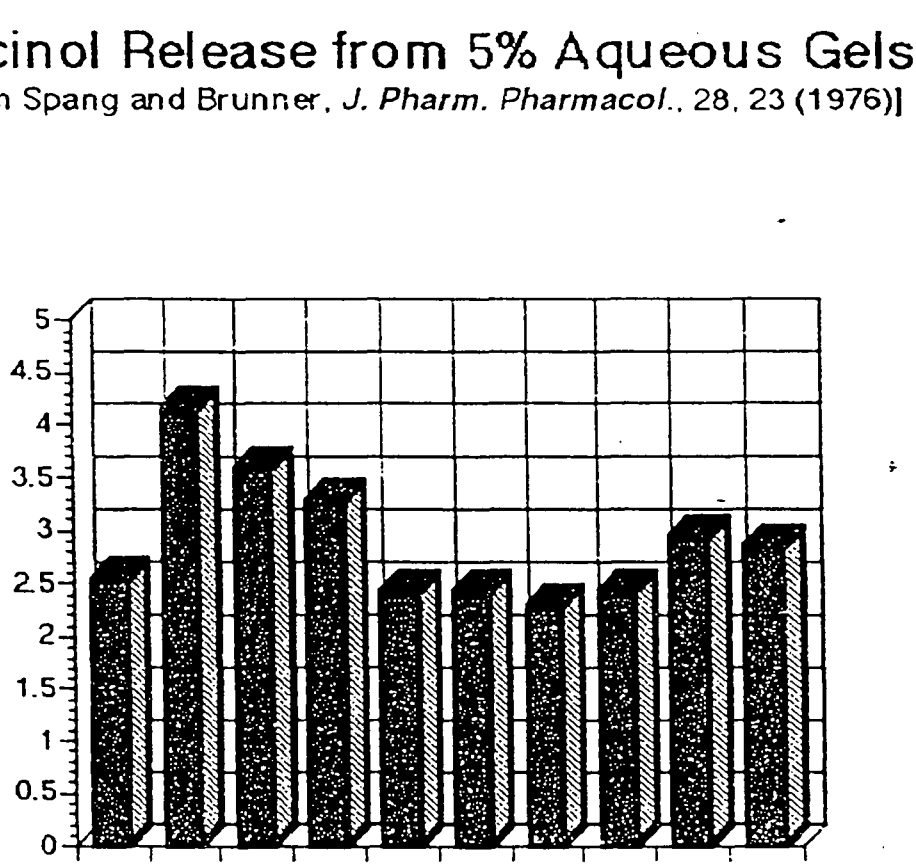


Figure 5. Benzocaine release from various gel formulations

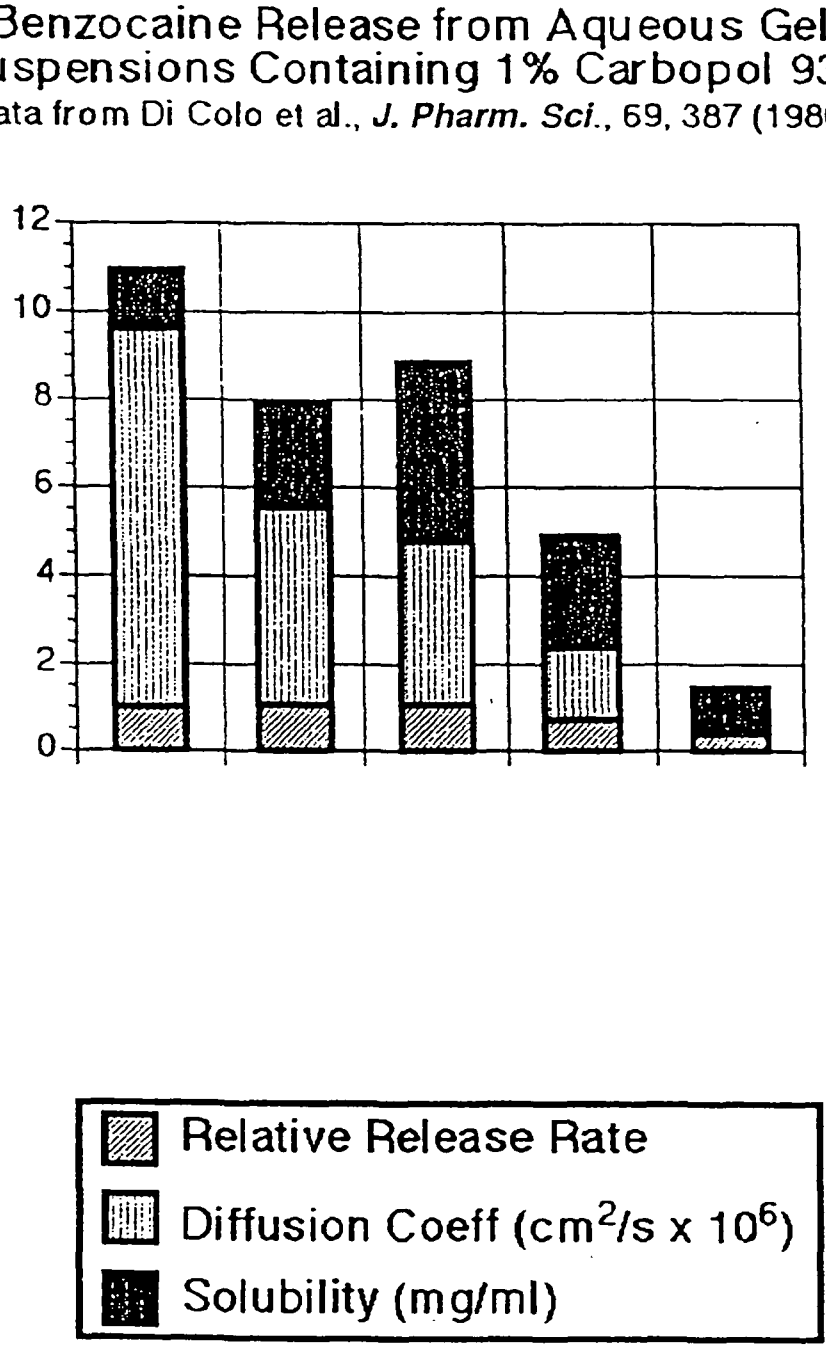


Figure 6. Skin penetration: solutions vs. gels

Hydrocortisone Flux from 0.2% Solutions
in 40% Isopropanol/Water
Gelling Agent: 1% Hydroxyethylcellulose
[Data from Shahi and Zatz, *J. Pharm. Sci.*, 67, 789 (1978)]

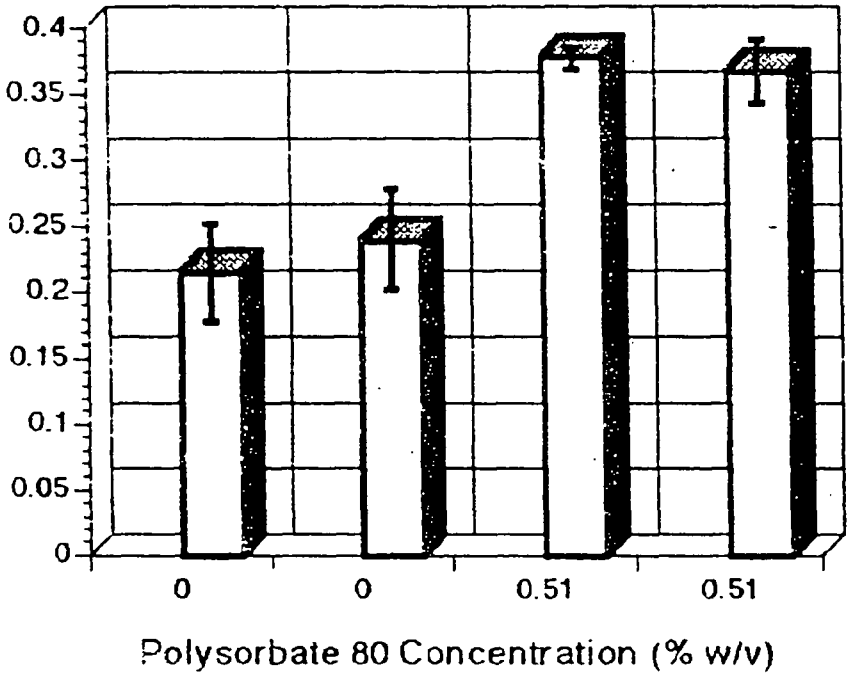


Figure 7. Clindamycin phosphate release from Altana and reference gels