

In Vitro Release of Clindamycin Phosphate: Effect of Viscosity

Steffany Gaffagan, Krista Witt, and Daniel Bucks, Ph.D.

Dow Pharmaceutical Sciences, Inc., Petaluma, CA 94954

Abstract

Purpose

In vitro release is used to characterize drug thermodynamics in topical dosage forms. This study was performed to demonstrate the differences in clindamycin phosphate (1%) thermodynamic activity in Clindagel® and Cleocin-T Gel® expected from their different viscosities, ~1500 versus >20000 cps, respectively. Clindagel employs a novel delivery system containing a lightly cross-linked polyacrylic acid polymer gelling agent whereas Cleocin-T Gel contains the standard carbomer 934P gelling agent.

Methods

This study was conducted in accordance with the FDA Scale-Up and Post-approval Changes guidance for semisolid dosage forms. Franz static diffusion cells, maintained at 32 °C, were assembled with hydrophilic (Tuffryn® .45mm pore) membranes. The receptor solution consisted of degassed 10% propylene glycol, 7.5% PEG 400, and 82.5% water (w/w/w). This composition was selected so as to approximate the liquid components comprising these clindamycin phosphate gel formulations and thereby limit effects of back diffusion of receptor fluid components into the gels. An infinite dose (~1 ml) of each formulation was applied. At 1, 2, 3, 4, and 6 hours from dosing, the entire receptor solution was collected and then analyzed for clindamycin phosphate concentration using an HPLC with UV detection.

Results

As predicted from the formulation differences, the release rate of clindamycin phosphate from Clindagel (1.0 ± 0.1 mg/hr^{1/2}) was significantly greater ($p = 0.0009$, unpaired t-test) than Cleocin-T Gel (0.6 ± 0.1 mg/hr^{1/2}).

Conclusions

Clindamycin phosphate release rate from Clindagel is significantly greater than Cleocin-T Gel, by almost two-times, and is consistent with differences in clinical efficacy and formulation composition between these two products. Greater release from Clindagel relative to Cleocin-T Gel is consistent with the equivalent clinical efficacy of once-daily dosing of Clindagel to that of twice-daily administration of Cleocin-T Gel in the treatment of acne.

Introduction

In vitro release studies can be used to assess performance characteristics of a finished topical dosage form. Subtle changes in the formulation that affect drug thermodynamics show up as a difference in drug release and may affect the clinical dosage regimen.

Drug release at steady-state from an infinite dose is proportional to the square root of time when the formulation controls the release process, i.e., when drug release is from a receding boundary.

Study Objective

The objective of this work was to demonstrate the expected difference in clindamycin phosphate release from two prescription non-alcoholic gels: A. (Clindagel® 1%, Galderma) and B. (Cleocin-T Gel® 1%, P&U) based upon differences in gelling agent characteristics and viscosity between the two formulations.

When gel A is used QD and gel B is used BID in patients with acne, comparable clinical efficacy and clindamycin plasma levels are achieved. These clinical observations (summarized below), further support an expected difference in clindamycin phosphate release between these two products.

Background

Gel A employs a novel, patented delivery system that contains a lightly cross-linked polyacrylic acid polymer gelling agent, Carbopol 981, that results in a looser polymer mesh network and a lower formulation viscosity relative to Gel B containing the standard carbomer 934P gelling agent.

Dow's Patented* Topical Delivery System

- Aqueous-based gels for delivering drugs into the skin
- Lightly cross-linked polyacrylic acid polymer gelling agent, Carbomer 981
- Loose mesh polymer network for optimal drug release
- Low viscosity, less than about 15,000 cps
- Broad functional pH of 3 to 9

*Dow et al., U.S. Patent Number 6,387,383 B1, 2002

Formulation Differences

A. Clindagel® 1% vs. B. Cleocin-T Gel® 1%

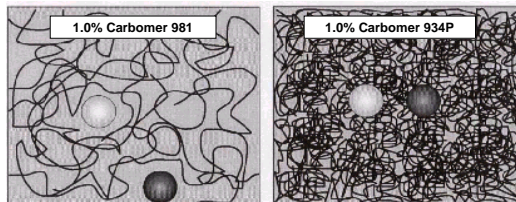
Carbomer grade and concentration:

- Clindagel: 0.2% Carbopol 981 (lightly crosslinked)
- Cleocin-T Gel: 0.6% Carbomer 934P (highly crosslinked)

Viscosity:

- Clindagel: ~1,500 cps
- Cleocin-T Gel: ~20,000 cps
- Propylene Glycol:
 - Clindagel concentration ~3 times higher than Cleocin-T Gel

Carbopol 981 & Carbomer 934P



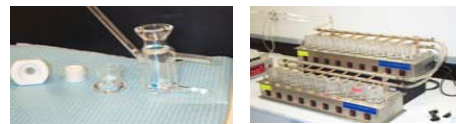
Methods

In Vitro SUPAC* Release Test

- Franz static cells (15mm dia., Crown Bio Scientific) containing a Tuffryn® membrane (Gelman Sciences) & degassed 10% PG : 7.5% PEG 400 : 82.5% water (by wt.) receptor fluid are equilibrated at 32 °C on a Franz cell console
- An infinite dose, ~1ml, of each gel is applied to six cells
- Donor compartment of each cell is capped to prevent evaporation
- Receptor fluid is collected at 1, 2, 3, 4, & 6 hrs post-dosing and analyzed for Clindamycin content by HPLC
- Clindamycin release rate is calculated for each cell
- Statistical analyses are conducted

* Guidance for Industry: Nonsterile Semisolid Dosage Forms. Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation. FDA, CDER May 1997

Franz Static Diffusion Cell & Franz Cell Console

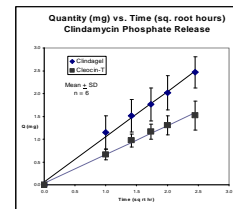
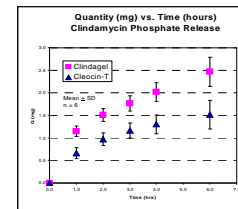


Results

In Vitro Release Test

The clindamycin phosphate release rate is the slope from a plot of the cumulative amount of clindamycin phosphate (Q) released into the receptor solution vs. the square root of time. The release rate of clindamycin phosphate from Clindagel (1.0 ± 0.1 mg/hr^{1/2}) was significantly greater ($p = 0.0009$, unpaired t-test) than from Cleocin-T Gel (0.6 ± 0.1 mg/hr^{1/2}).

Clindamycin phosphate release rates from Clindagel and Cleocin-T Gel were then analyzed using the Wilcoxon Rank Sum/Mann-Whitney statistical test as described in the FDA's SUPAC guidance. The rate of clindamycin phosphate release from Clindagel was significantly greater ($p < 0.05$) than from Cleocin-T Gel based upon this statistical evaluation.



Acne Clinical Study Results*

- 12-Week Acne Clinical Study (667 patients) comparing two topical clindamycin gels.
- Clindagel (QD) was comparable to Cleocin-T Gel (BID) in treatment of mild to moderate acne vulgaris in global severity scores and various acne lesion counts (for example, 54% vs 53%, respectively, in inflammatory lesion count reduction).
- Clindagel (QD) was tolerated better than Cleocin-T Gel (BID).

*Rizer, et al., American Academy of Dermatology 59th Annual Meeting, P69, 2001

Absorption Study Results

5-Day Absorption Study in 24 Acne Patients: Clindagel QD vs. Cleocin-T BID Applied to Face, Chest and Back

Blood Sample Clindamycin Concentration (ng/ml)

	Clindagel, QD		Cleocin-T, BID		ANOVA P-Value (for 0-24 hr AUC)
	Mean	Std. Dev.	Mean	Std. Dev.	
Day 1	17.0	14.8	11.8	13.9	0.38
Day 5	23.8	26.5	22.9	18.6	0.92

Conclusion

- As anticipated, this study demonstrates that the rate of clindamycin phosphate release from Clindagel is significantly greater than from Cleocin-T Gel.
- The difference in clindamycin phosphate release rate is consistent with acne clinical data post administration of Clindagel, QD, and Cleocin-T Gel, BID. Study results demonstrate:
 - Comparable clinical efficacy for global severity scores and lesion count reduction
 - Comparable clindamycin plasma levels
- Higher drug release from Clindagel is expected due to the lower viscosity & polymer cross-linking achieved with this formulation approach. Lowering viscosity & polymer cross-linking corresponds to a higher drug diffusion coefficient within a formulation.

Dow Pharmaceutical Sciences, Inc.
Skin Biology & Drug Delivery
1330 Redwood Way
Petaluma, CA 94954
707-793-2600
www.dowpharmsci.com

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