CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 50-709

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

W/LA -

MAY 22 2000

Clinical Pharmacology/Biopharmaceutics Review

NDA: 50-769 SUBMISSION DATE: 1/27/2000

PRODUCT: Benzamycin® ——
(Benzoyl Peroxide 5% gel/Erythromycin 3% gel)

SPONSOR: Dermik Labs, Inc.
Collegeville, PA REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA

I. BACKGROUND

Drug Classification: 3S

Dosage Form: Gel for topical application (Benzoyl peroxide 5% and Erythromycin 3%)

Indication: For the topical treatment of acne vulgaris

Pharmacologic Class: Benzamycin® —— contains both 3% erythromycin and 5%benzoyl peroxide. Erythromycin is an antibiotic produced from a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythreus*). Benzoyl Peroxide is an antibacterial and oxidizing agent. Both ingredients are active against *P. acnes*.

Dosage and administration: Applied topically twice daily.

Foreign marketing history: The same combination has been used clinically for more than a decade as Benzamycin® Topical Gel, NDA # 50-557.

Formulation: Benzamycin® —— is provided as a Dual Pouch that was developed by the sponsor as a more convenient, room temperature stable alternative to Benzamycin® Topical Gel. The current Benzamycin product requires compounding by a pharmacist, and refrigerated storage by the patient to maintain stability of the active ingredients.

The dual gel product (0.8g/pouch) is designed such that the two active gels, a —erythromycin and a — benzoyl peroxide, are packaged in separate chambers of a single-use, dual dispensing

pouch, thereby maintaining the stability of the active ingredients over long term room temperature storage. The patient would empty the pouch to deliver equal portions of both active gels into the palm. With a fingertip, the patient will blend the two gels together according to the product instruction. The formulation after mixing by the patient is presented in the following table.

Ingredient	%w/w
Erythromycin, USP	
Hydrous benzoyl peroxide, USP	
Carbomer 934,NF	
Sodium Hydroxide, NF	
Dioctyl sodium sulfosuccinate 75%, DF	
Purified water, USP	
Hydroxypropyl cellulose, NF	
SD Alcohol #40-B/190°	

II. RECOMMENDATION

The sponsor has demonstrated extremely low systemic exposure of erythromycin upon topical application of Benzamycin after either 1 or 3 units (pouches) of applications. The information provided in this application meets the requirements of the Office of Clinical Pharmacology and Biopharmaceutics. The labeling changes on page 8 of the review should be conveyed to the sponsor.

TABLE OF CONTENTS

II. ANALYTICAL VALIDATION

- **Is the Analytical validation of erythromycin adequate?**

The analytical validation for erythromycin provided by the sponsor is acceptable and has been summarized below.

[redacted]

IV. PHARMACOKINETIC STUDIES

- **Has the sponsor evaluated the systemic exposure of erythromycin upon topical application under maximal use conditions in acne patients?**

The sponsor has conducted a study to assess the topical and systemic tolerance to and the bioavailability of erythromycin from a 0.8 g application of 3% erythromycin/ 5% benzoyl peroxide gel after a single (1x) application in 8 acne patients and after 2.4 g (3x) application in 8 acne patients. The to-be marketed dosage is twice daily, i.e. a total of 1.6 g (2x). The study results are described below.

Single dose pharmacokinetics of topical 3% erythromycin/ 5% benzoyl peroxide gel in patients diagnosed with acne vulgaris (DL-6026-9717)

Investigator

[redacted]

This is an open-label, single-dose, topical and systemic tolerance, pharmacokinetic study in 16 patients (6M & 10 F) of at least 18 years of age. The patient demographics are

attached in the Appendix on page 10. 8 Patients had both facial and back acne, while the other 8 had only facial acne. On Day 1, 0.8 g of compounded product (Lot #97J003) was applied to the face (approximate 225 cm^2 area) by the site personnel. For the 8 patients with back acne, two additional 0.8 g of compounded product were applied, one to each side of the upper back (550 cm^2 on each side and total dose of 2.4 g). The contents the pouch were blended together for 5 minutes using circular motions with a gloved finger. The face was not washed or the applied dose removed until 24 hours after application of the drug. Blood samples were collected predose and at 0.5, 1, 2, 4, 6, 8, 12 and 24 hours following the drug application.

All pharmacokinetic samples analyzed for erythromycin were BLQ except 1 sample (subject 7 at 8 hours post dose) from 0.8 g dose group. This concentration was 2.04 ng/ml (LOQ being 2 ng/ml). No patients with the 2.4 g dose had detectable levels.

Conclusions

There appears to be no detectable systemic absorption of erythromycin following a single 0.8 g application to the face or following three single 0.8 g applications to the face and back.

Benzoyl peroxide is converted to benzoic acid after absorption. Benzoic acid is used as a preservative in various food items, hence, evaluation of benzoic acid will not be discriminatory. The sponsor has therefore not evaluated the concentration of benzoic acid.

V. IN VITRO STUDIES

- **Has the in vitro skin permeation of Benzamycin Topical gel been compared to the to-be marketed formulation?**
- **Has the in vitro release of erythromycin and benzoyl peroxide been evaluated?**
- **Does the degree of mixing have any influence on the release pattern?**

The sponsor has conducted both in vitro skin permeation of erythromycin through human cadaver skin as well as in vitro release experiments. No definitive conclusions can be drawn from the skin permeation experiment. The in vitro experiments have been reviewed for monitoring post approval changes in future, especially the in vitro release profile. The in vitro experiments are discussed in this section.

Study: Skin permeation of erythromycin from various gel formulations

Skin permeation from the following gel formulations was compared along with the marketed benzamycin. The formulations used are given in the following table.

Ingredient	VEM1-43A*	VEM1-43B	VEM1-43C
Erythromycin	6.9	6.9	6.9
SD Alcohol			
Hydroxypropylcellulose			

* to-be-marketed formulation

Erythromycin absorption for the formulations is tabulated below (data from 6 replicates).

Formulation	Mean amount of erythromycin applied to the skin (μg)	Mean amount of erythromycin absorbed at 24 hrs	% Absorbed at 24 hrs.
Benzamycin	117.2	6.7	5.8
VEM1-43A	120.0	6.3	5.3
VEM1-43B	122.4	9.0	7.4
VEM1-43C	131.5	11.1	8.5

This shows that the mean amount of absorbed erythromycin was different among the various formulations and appeared to increase with the increase in content. However, when comparing data after three replicates as compared to 6 replicates, no definitive trend could be obtained in terms of the mean amount of erythromycin absorbed from the various formulations. This shows that the number of replicates plays a role in deciding the trend, hence, may not be a very reliable method to obtaining any conclusions.

The following figure shows the mean amount of erythromycin in the receptor fluid, which does not reflect the same trend as seen with the mean amount absorbed. Hence, it will also be misleading to only rely on the mean amount of drug in the receptor fluid, without taking into consideration the contribution of the drug within the skin to the total amount absorbed and also the slopes of the curves.

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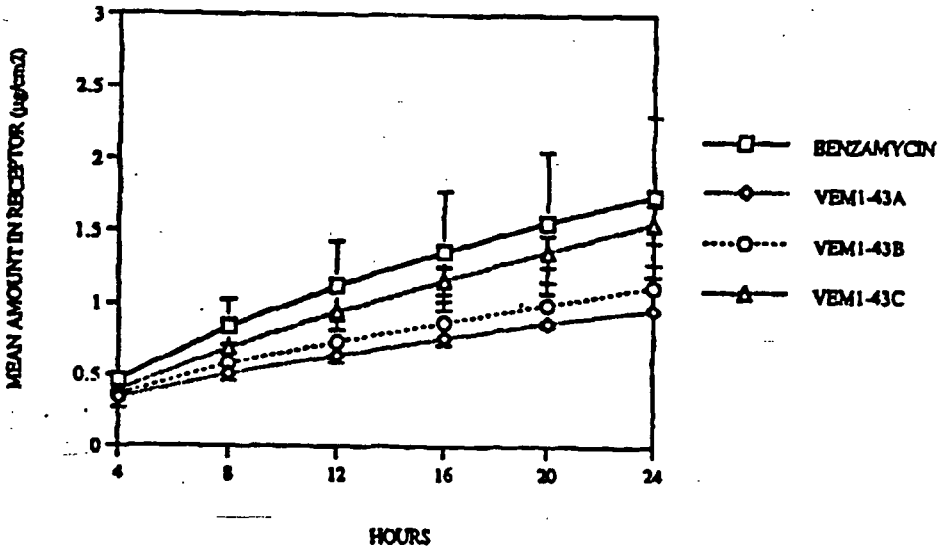

The detailed absorption and the contribution of the stratum corneum, viable skin and receptor fluid to the total amount absorbed is shown in the table below for Benzamycin (marketed) and the to-be-marketed formulation. After 24 hours, the skin was washed and stripped with Scotch tape for analyzing the drug remaining in the stratum corneum

Formulation	Benzamycin Gel (n=6)	VEM1-43A Gel (n=6)
Compound measured	^{3}H-Erythromycin	^{3}H-Erythromycin
Amount applied to the skin (µg)	117.2	120.0
Stratum Corneum (µg)	2.54	3.14
Viable Skin (µg)	3.10	2.60
Receptor Fluid (µg)	1.11	0.611
Amount Absorbed (µg)[a]	6.75	6.35
Total Absorption (%)	5.8%	5.3%
Amount in the skin (µg)[b]	5.64	5.74
% in the Skin[c]	4.8%	4.8%
[a]stratum corneum + viable skin + receptor fluid [b]stratum corneum + viable skin [c]mean amount in skin/mean amount applied to skin		

Conclusions

- Erythromycin permeation into and through the skin is low.
- There was similar percutaneous absorption (5.8% and 5.3%) between the marketed Benzamycin and the to-be marketed formulation.

- The majority of absorbed erythromycin resides within the skin (stratum corneum plus viable tissue).
- The amount of absorption correlated with the increasing concentration of glycol, but depended on the number of replicated evaluated.

Reviewer's Comment

Due to the various factors involved, as explained earlier, no definitive conclusions should be drawn from this in vitro experiment regarding the in vitro permeation of erythromycin. However, in general we could say that erythromycin permeation through the skin is low.

Study: In vitro release of erythromycin and benzoyl peroxide from gel formulations

This in vitro experiment was performed in order to assess the effects of different mixing protocols ('poorly mixed vs. 'well mixed') on the in vitro release of erythromycin from the dosage form. To prepare the 'well mixed' sample: erythromycin gel and benzoyl peroxide gel in a ratio of 1:1 was combined by vortex mixing for 15 minutes and then spiked with ^{3}H erythromycin and ^{14}C labeled benzoyl peroxide. To prepare the 'poorly mixed' samples, individual erythromycin and peroxide gel was spiked with ^{3}H erythromycin and ^{14}C peroxide by vortex mixing. After equilibration the individual gels were applied to the test membrane and mixed together for 5 seconds using a glass rod. A total of 600 mg/cm^2 was applied to each one cm^2 membrane.

The cumulative amount released was plotted against the square root of time. The slope of the linear portion was used as an index of release.

The tables showing cumulative release and the figures of the in vitro release are attached in the Appendix on pages 11-18.

Benzoyl peroxide release from the 'well mixed' samples are linear where as the release profile for erythromycin was slightly curved. Thus two slopes can be assigned to erythromycin release. A possible explanation could be that dispersed benzoyl peroxide particles could retard the diffusion of erythromycin, which then picks up somewhat as benzoyl peroxide near the membrane surface is itself cleared from the gel.

In the 'poorly mixed' samples a wide variability is seen. This could be because some particles of erythromycin may be near the cell membrane whereas the others maybe separated from it because of the benzoyl peroxide in the gel. The figures showing the variability in the release of erythromycin and benzoyl peroxide in the poorly mixed samples are attached in the Appendix on pages 19-20.

Conclusions

- The results demonstrated that the major difference between the 'well mixed' and the 'poorly mixed' samples was in the variability of release rather than the rate of release. This was due to the unequal amounts of individual active gel being in contact with the membrane.
- The relevance of this data is difficult to ascertain in clinical situations. The in vitro testing was conducted using a thick mass of gel (600 mg/cm^2), where as the clinical dose is approximately 4 mg/ cm^2 (≅ 80 mg over a ≅ 225 cm^2 surface area of the face).

VI. OVERALL CONCLUSIONS

The systemic exposure of erythromycin from Benzamycin ——— is very low. Only one patient out of 16 showed a detectable level, which was only 0.04 ng/ml above the limit of detection (LOQ 2 ng/ml).

VII. LABEL

The underlined portion has been added to the label.
The second sentence under "Pharmacokinetics" subsection should read as follows:

In a single dose pharmacokinetic study of Benzamycin® ———
——— virtually no systemic.....

/S/ 22/00

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. /S/

CC: NDA 50-769
HFD-540/Div File
HFD-540/CSO/Cross
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

APPENDIX

NDA 50-769

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LISTING 4. DEMOGRAPHICS BY PATIENT AND BASELINE CHARACTERISTICS

PATIENT NUMBER	AGE (YEARS)	RACE	SEX	HEIGHT (CM)	WEIGHT (KG)	PILLSBURY CLASSIFICATION
001	18	White	Male	178.5	68.9	Grade III
002	21	White	Male	176.8	66.4	Grade III
003	18	White	Female	166.5	60.7	Grade III
004	37	White	Female	165.4	71.9	Grade II
005	30	Hispanic	Female	162.4	72.1	Grade II
006	30	White	Female	167.5	72.5	Grade III
007	28	White	Female	175.0	76.3	Grade I
008	23	Black	Female	164.0	64.7	Grade I
009	19	Hispanic	Male	168.5	62.1	Grade III
010	30	White	Male	177.5	85.1	Grade III
011	25	White	Male	184.0	85.2	Grade III
012	21	White	Male	184.0	71.6	Grade III
013	23	White	Female	164.0	63.4	Grade II
014	21	White	Female	167.0	59.9	Grade II
015	20	Hispanic	Female	161.0	61.5	Grade II
016	37	Asian	Female	157.0	53.3	Grade II

† Pillsbury Classification:
Grade I: Consists mainly of comedones, with an occasional small inflamed pustule.
Grade II: Inflammatory papules/pustules are more numerous, though ordinarily they are confined largely to the face.
Grade III: Acne, more papules and pustules with occasional larger lesions, which spread to upper shoulders, back and chest.
Grade IV: Consists mostly of lesions with large, painful, and systic, involving the face, neck and upper trunk.

Table 1. Data for well-mixed gels								
	1A. Erythromycin			well-mixed				
	Cumulative amount released (mg/cm^2)							
√t ($h^{0.5}$)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6	Mean	sem
0.5744563	4.02757	3.30024	3.49357	3.4323	3.6687	3.3136	3.54	0.11207
0.8124038	7.39487	6.53209	6.49467	6.5391	6.9447	7.09735	6.83	0.1516
1	10.0796	9.40937	8.84004	9.2707	9.6053	10.3705	9.60	0.227
1.1532563	12.6137	11.9101	10.9834	11.692	11.974	13.2938	12.08	0.3241
1.2884099	14.9299	14.1915	13.0278	13.926	14.34	16.0624	14.41	0.41626
1.4142136	17.1079	16.3903	15.0143	16	16.505	18.626	16.61	0.49294
1.5811388	20.1203	19.778	17.7147	19.08	19.599	22.0941	19.73	0.58436
1.7320508	23.0099	22.7993	20.3278	21.97	22.574	25.2903	22.66	0.65787
1.8708287	25.571	25.7066	22.8338	24.765	25.421	28.451	25.46	0.73938
2	28.2503	28.4506	25.2587	27.399	28.203	31.4865	28.17	0.81967
2.1213203	30.8466	31.0118	27.5756	30.122	30.941	34.5773	30.85	0.91613
2.236068	33.5008	33.7468	29.8326	32.758	33.781	37.8812	33.58	1.05346
2.3452079	36.1519	36.4547	32.163	35.354	36.628	40.856	36.27	1.13891
2.4494897	38.9763	39.254	34.6385	38.111	39.841	43.9863	39.13	1.22936
2.5495098	41.9728	42.2544	37.2533	40.793	42.985	47.2276	42.08	1.32051
2.6457513	44.8984	45.3771	39.7961	43.699	46.097	50.4391	45.05	1.41065
2.7386128	47.7953	48.2938	42.2462	46.588	49.388	53.6607	48.00	1.51876
2.8284271	50.6352	51.2582	44.7734	49.506	52.66	56.9522	50.96	1.62662
Slope	26.28	26.74	22.94	25.77	28.50	29.80	26.67	0.96665
R^2	0.99	0.99	0.99	0.99	0.99	1.00	0.99	
Slope from averaged data:			25.95		R^2 =	0.99		

	1B. Benzoyl Peroxide			well-mixed				
	Cumulative amount released (mg/cm^2)							
√t ($h^{0.5}$)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6	Mean	sem
0.5744563	11.93	10.83	10.67	10.45	11.08	10.86	10.95	0.21496
0.8124038	19.71	18.83	17.66	18.10	18.79	20.15	18.87	0.38322
1	25.41	25.24	22.75	23.81	24.64	27.13	24.83	0.61105
1.1532563	30.43	30.37	27.08	28.43	29.55	32.90	29.79	0.80994
1.2884099	34.93	34.72	30.83	32.58	34.07	37.86	34.16	0.96945
1.4142136	38.84	38.72	34.35	36.36	38.09	42.44	38.13	1.10831
1.5811388	44.15	44.39	39.07	41.43	43.74	48.47	43.54	1.28827
1.7320508	49.03	49.13	43.33	46.04	48.74	53.92	48.37	1.44693
1.8708287	53.19	53.70	47.22	50.24	53.47	58.85	52.78	1.58905
2	57.25	57.76	50.80	54.05	57.84	63.32	56.84	1.71562
2.1213203	61.11	61.49	54.14	57.75	61.96	67.68	60.69	1.85107
2.236068	64.88	65.14	57.34	61.12	66.05	71.92	64.41	2.00552
2.3452079	68.47	68.55	60.39	64.32	70.01	75.87	67.94	2.1439
2.4494897	72.20	72.10	63.63	67.68	74.04	79.91	71.59	2.26949
2.5495098	75.86	75.62	66.78	70.88	78.06	83.93	75.19	2.41299
2.6457513	79.40	79.08	69.77	74.05	81.85	87.80	78.66	2.5468
2.7386128	82.75	82.49	72.68	77.25	85.60	91.61	82.07	2.68083
2.8284271	85.99	85.75	75.53	80.33	89.15	95.30	85.34	2.80271
Slope	34.42	33.42	29.61	31.31	37.45	38.13	34.06	1.36673
R^2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	
Slope from averaged data:			33.32		R^2 =	1.00		

Table 2. Data for poorly-mixed gels.

	2A. Erythromycin			poorly-mixed				
	Cumulative amount released (mg/cm^2)							
√t ($h^{0.5}$)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6	Mean	sem
0.57	0.00	0.00	5.66	0.50	1.01	1.45	1.44	0.876657
0.81	0.00	0.00	10.20	2.89	5.41	9.17	4.61	1.808943
1.00	0.00	0.00	13.63	8.49	14.62	29.68	11.07	4.536322
1.15	0.00	0.02	16.63	15.98	26.83	43.14	17.10	6.729054
1.29	0.00	0.06	20.53	25.14	42.67	51.16	23.26	8.651362
1.41	0.05	0.15	24.07	35.50	58.24	57.74	29.29	10.67345
1.58	0.19	0.37	28.69	52.43	71.56	66.13	36.56	12.96935
1.73	0.53	0.72	33.37	70.44	81.60	73.32	43.33	15.10471
1.87	1.00	1.27	38.22	92.27	90.60	79.57	50.49	17.53309
2.00	1.58	1.98	43.14	120.40	98.39	85.87	58.56	20.6899
2.12	1.65	2.87	48.02	136.01	106.07	91.87	64.42	22.81219
2.24	2.43	3.88	52.53	150.26	113.79	97.98	70.15	24.75562
2.35	3.22	5.08	58.06	163.64	114.57	104.11	74.78	26.20379
2.45	4.11	6.64	64.33	177.00	122.46	109.84	80.73	27.97896
2.55	5.25	8.61	70.89	190.04	129.69	116.13	86.77	29.65023
2.65	6.39	10.79	77.19	201.63	136.69	122.24	92.49	31.12956
2.74	7.58	13.15	83.67	212.34	143.34	128.95	98.17	32.48927
2.83	8.94	15.63	90.23	221.91	149.75	135.62	103.68	33.67995
Slope	10.27	18.15	60.64	122.81	61.99	61.49	55.89	16.40593
R^2	0.99	0.98	1.00	1.00	0.99	1.00		
Slope from averaged data:			55.89		R^2=	1.00		

	2B. Benzoyl Peroxide			poorly-mixed				
	Cumulative amount released (mg/cm^2)							
√t ($h^{0.5}$)	Cell 1	Cell 2	Cell 3	Cell 4	Cell 5	Cell 6	Mean	sem
0.57	15.17	16.30	10.23	0.00	0.06	0.32	7.01	3.191164
0.81	24.18	26.23	16.40	0.06	0.69	2.13	11.62	4.958501
1.00	30.34	32.67	21.03	0.33	2.26	7.47	15.68	5.817652
1.15	35.42	37.95	24.79	0.87	4.65	12.36	19.34	6.43114
1.29	39.91	42.38	28.29	1.66	8.51	15.88	22.77	6.84355
1.41	44.09	46.28	31.33	2.69	13.10	18.84	26.05	7.136381
1.58	49.54	51.51	34.90	4.66	18.17	22.85	30.27	7.530853
1.73	54.28	56.12	38.08	6.98	22.36	26.35	34.03	7.833713
1.87	58.07	60.20	40.87	9.83	26.26	29.52	37.46	7.969878
2.00	61.37	63.91	43.29	13.98	29.70	32.58	40.81	7.901863
2.12	64.64	67.11	45.46	16.49	33.05	35.39	43.69	7.984288
2.24	67.30	69.98	47.36	18.94	36.32	38.20	46.35	7.993742
2.35	69.55	72.87	49.51	21.17	39.47	40.64	48.90	8.007735
2.45	71.66	75.91	51.93	23.45	42.69	43.25	51.48	8.031574
2.55	74.18	78.98	54.23	25.59	45.76	45.77	54.08	8.111473
2.65	76.32	82.11	56.37	27.67	48.78	48.25	56.58	8.180469
2.74	78.26	85.10	58.45	29.64	51.75	50.81	59.00	8.234892
2.83	80.30	87.95	60.53	31.49	54.65	53.48	61.40	8.29729
Slope	22.12	29.74	21.69	21.28	30.61	25.30	25.12	1.703282
R^2	1.00	1.00	1.00	1.00	1.00	1.00		
Slope from averaged data:			25.12283		R^2=	1.00		

Fig. 1. ERYTHROMYCIN IN WELL MIXED SAMPLES

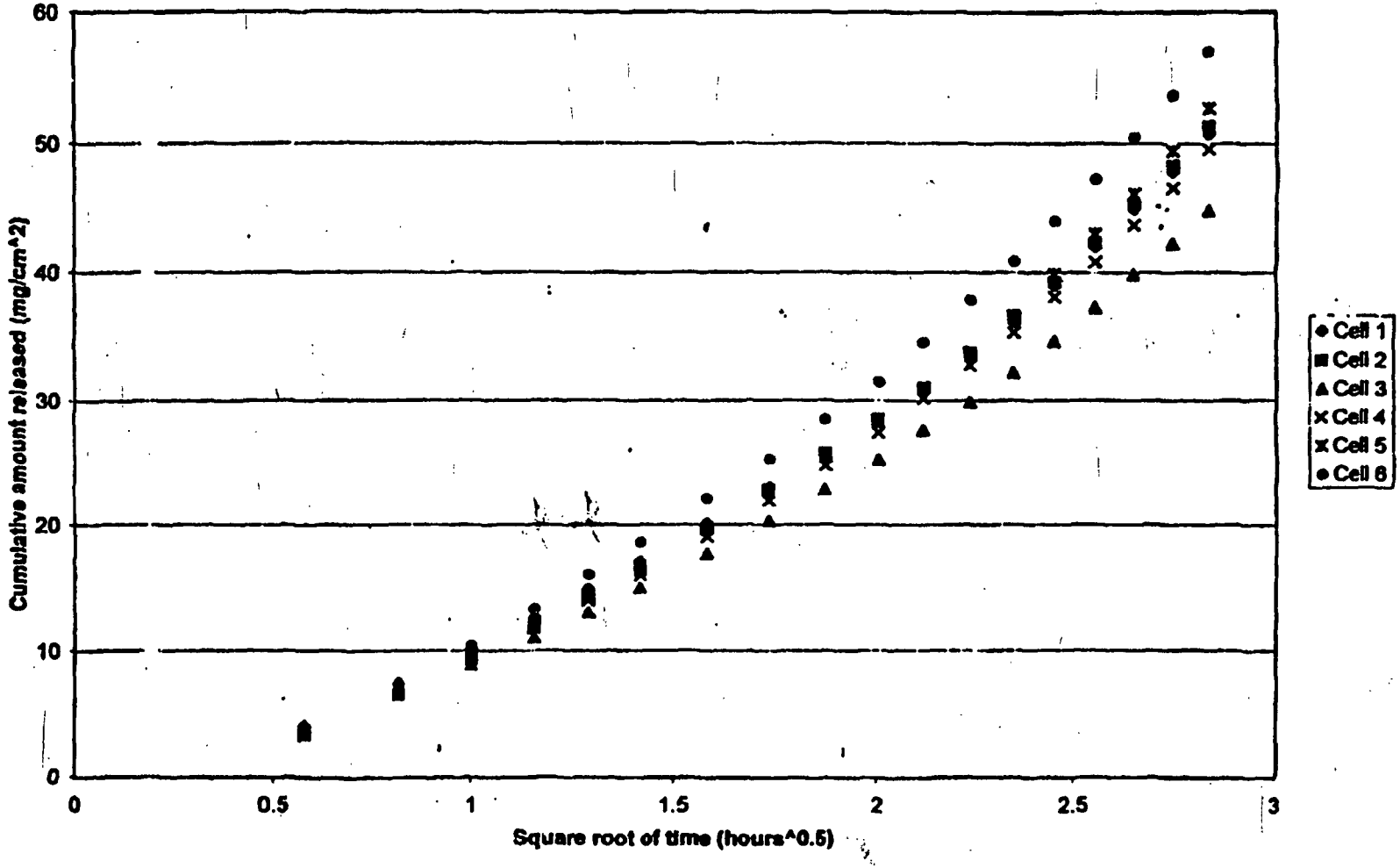

Fig. 2. BENZOYL PEROXIDE IN WELL MIXED SAMPLES

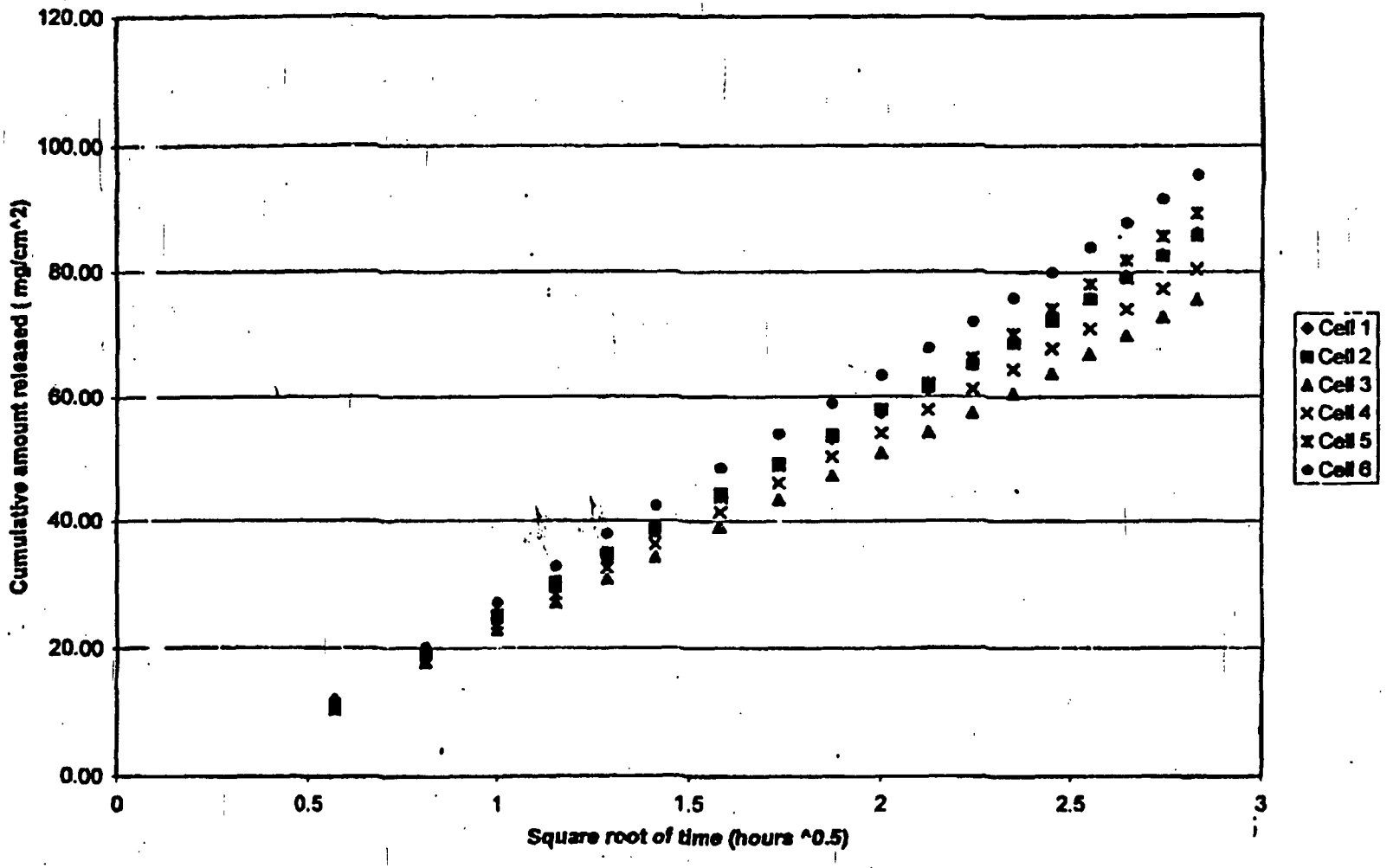

Fig. 3. ERYTHROMYCIN IN POORLY MIXED SAMPLES

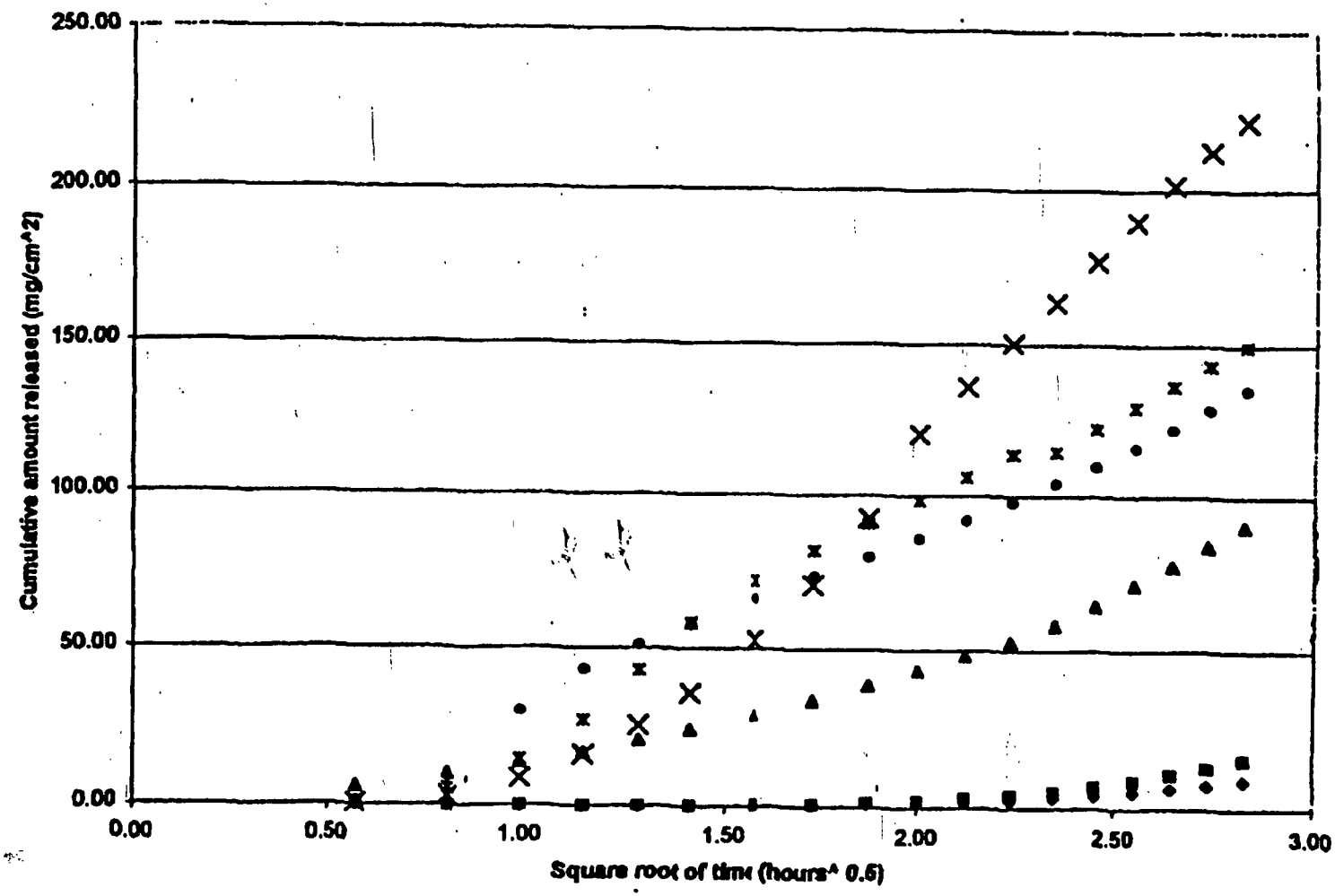

Fig. 4. BENZOYL PERCXIDE IN POORLY MIXED SAMPLES

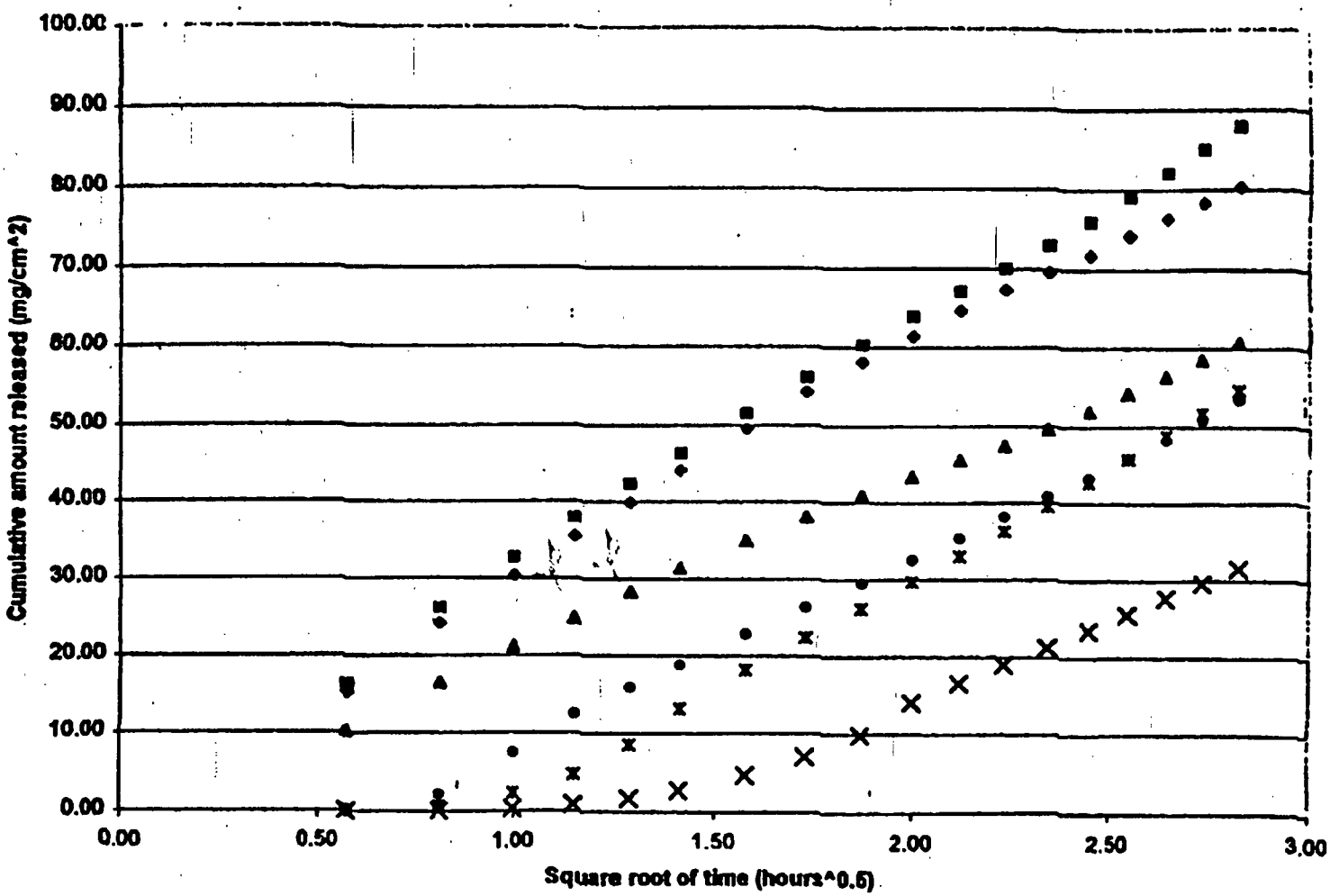

Fig. 5. COMPARISON OF ERYTHROMYCIN IN WELL MIXED AND POORLY MIXED SAMPLES