CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20802

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JUL 2 2 1997

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20,802 **Submission Date:** 1/15/97

Generic Name and Strength: Combination Product: Acetylsalicylic acid/Acetaminophen/Caffeine 250/250/65 mg

Dosage Forms: Tablets, Caplets, Geltabs.

Brand Name: Excedrin® Extra Strength **Date Assigned:** 1/27/97

Applicant: Bristol-Myers Products **Final Review Date:** 7/2/97

Submission Code: 3S **Reviewer:** Kofi A. Kumi, Ph.D.

SYNOPSIS:

The applicant submitted a new drug application seeking approval for Over the Counter (OTC) use of Excedrin® Extra Strength (EES) Tablets, Caplets and Geltabs for the temporary relief of pain associated with migraine headaches. EES is a combination product containing active ingredients of acetylsalicylic acid, acetaminophen and caffeine 250/250/65 mg. EES tablets, caplets and geltabs have been on the OTC market for 18, 10 and 2 years, respectively. In a 9/13/96 meeting, the applicant was advised by the agency to conduct bioequivalence study to demonstrate the tablets used in the clinical studies are bioequivalent to the various EES formulations on the market.

A single center, open label, single dose, randomized 3-way crossover bioequivalence study was conducted to demonstrate EES tablets are bioequivalent to EES caplets and geltabs. Twenty nine healthy male subjects were administered either 2 EES tablets, 2 EES caplets or 2 EES geltabs during a dosing period. The 90% confidence interval (CI) for Ln transformed Cmax and AUC∞ are contained in the tables below.

Caffeine: 90% Confidence Intervals

Treatment	Ln Cmax	Ln AUC (0-∞)
Caplets vrs Tablets	89.4% - 97.2% (0.93*)	92.2% - 101% (0.96*)
Geltabs vrs Tablets	89.4% - 97.2% (0.94*)	93.1% - 102% (0.97*)

(*) Point estimate

Total Salicylate: 90% Confidence Intervals

Treatment	Ln Cmax	Ln AUC (0-∞)
Caplets vrs Tablets	94.5% - 108% (1.01*)	94.6% - 102% (0.98*)
Geltabs vrs Tablets	94.5% - 108% (1.01*)	90.7% - 97.8% (0.94*)

(*) Point estimate

Acetaminophen: 90% Confidence Intervals

Treatment	Ln Cmax	Ln AUC (0-∞)
Caplets vrs Tablets	88.4% - 100% (0.94*)	93.4% - 99.2% (0.96*)
Geltabs vrs Tablets	90.9% - 103% (0.96*)	92.9% - 98.7% (0.96*)

(*) Point estimate

The 90% CI for Ln AUC∞ and Ln Cmax were contained within the regulatory criteria for bioequivalence. EES caplets was demonstrated to be bioequivalent to EES tablet. EES geltabs was also demonstrated to be bioequivalent to EES tablet. The 3 EES products could therefore be used interchangeably. The applicant reported no clinically significant safety findings that was directly attributed to Excedrin® ES.

RECOMMENDATION:

The Bioequivalence study submitted under the Human Pharmacokinetics and Bioavailability Section of NDA 20,802 demonstrated that Excedrin® Extra Strength tablets, caplets and geltabs are bioequivalent and supports a recommendation for approval for the use of these Excedrin® ES products interchangeably.

TABLE OF CONTENTS:

REVIEW:

Background:

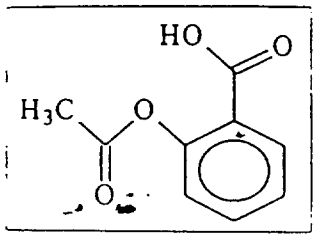
This review contains a summary of the study submitted to section 6 (Human Pharmacokinetics and Bioavailability) in support of NDA20,802. In a 9/13/96 meeting, the applicant was advised by the agency to conduct bioequivalence study to demonstrate the tablets used in the clinical studies are bioequivalent to the various EES formulations on the market. Currently, EES is marketed as an OTC product for the temporary relief of the pain of headache, sinusitis, colds, muscular aches, menstrual discomfort, toothache and for minor arthritis pain. The pivotal clinical studies in support of this application were conducted using EES tablets. EES tablets, caplets and geltabs have been on the OTC market for 18,10 and 2 years, respectively. The applicant is seeking approval for the use of EES in the treatment of the pain associated with migraine headache.

The pathophysiology of migraine may be of neurogenic and/or vascular origins. Current therapies for migraine include ergotamine tartrate alone or in combination with caffeine, dihydroergotamine mesylate (DHE 45) and sumatriptan succinate. These therapies are expensive, have significant adverse effects and available only with prescription. The applicant indicated that an OTC product, such as Excedrin® ES that is indicated for the relief of pain associated with migraine will be beneficial to patients when they have migraine attacks.

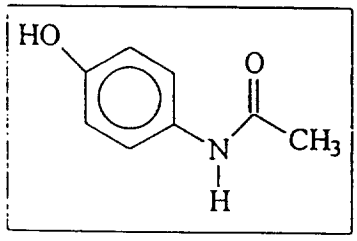
Excedrin® ES is an internal analgesic combination product which contains aspirin (acetysalicyclic acid) 250 mg, acetaminophen 250 mg and caffeine 65 mg in each tablet, caplet and geltab. Aspirin is a salicylate used as an analgesic, antipyretic and anti-inflammatory. Acetaminophen, an active metabolite of phenacetin, is an analgesic-antipyretic agent. Caffeine is a methylated xanthine whose pharmacological actions include relaxation of smooth muscle, stimulation of central nervous system, cardiac muscle and acts on the kidney to produce diuresis.

Physicochemical Properties:

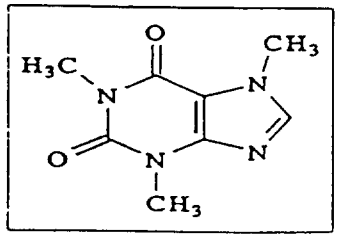
Structures of active ingredients are provided below:



Aspirin



Acetaminophen



Caffeine

Molecular Formula:

Aspirin: $C_9H_8O_4$ Acetaminophen: $C_8H_9NO_2$ Caffeine: $C_8H_{10}N_4O_2$

Formulation:

The composition of the compressed cores are the same for the tablets, caplets and geltabs and is provided below:

Composition	mg/tab
acetaminophen, USP	250
aspirin, USP	250
caffeine, USP	65

The composition of the coatings for the tablets, caplets and geltabs are provided in the appendix.

Dissolution: The USP requirements for dissolution rate for Excedrin active ingredients are as follows:
Apparatus: USP Apparatus 2
Q = 75%
Paddle Speed: 100 rpm
Run Time: 45 mins
Medium: 900 mL purified water at 37°C

The dissolution of the core tablets met the USP criteria for Excedrin ES; the dissolution data are contained in the appendix. The samples were analyzed using a

Uses (per draft label): For temporary relief of pain associated with:
Headache including Migraine Headache,Toothache, Muscular Aches, Backache, Colds, Minor Arthritis and Menstrual Discomfort.

Directions (per draft label): Adults: 2 (insert dosage form) with water every 6 hours while symptoms persist, not to exceed 8 (insert dosage form) in 24 hours or as directed by a doctor. **Children:** Do not give to children under 12 unless directed by a doctor.

Analytical Method:

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OVERVIEW OF BIOEQUIVALENCE STUDY:

Study CRP 116-01-95: Bioavailability Study of Three Combination Analgesic Formulations: Excedrin Tablets, Excedrin Caplets and Excedrin Geltabs (Vol. 10 page 000325, Vol. 8 page 00014)

Introduction: Excedrin Extra Strength (EES) is an Over The Counter (OTC) product currently approved to be used for temporary relief of the pain of headache, sinusitis, colds, muscular aches, menstrual discomfort, toothaches and minor arthritis pain. The applicant submitted a new drug application for EES to be used for the pain associated with migraines. The clinical study for this indication was conducted using EES tablets; however, there are 3 products of EES on the OTC market- Excedrin Extra Strength tablets, Caplets and Geltabs. The purpose of this study was to demonstrate that the three EES products are bioequivalent. The clinical study was conducted at

. and the data analysis for the bioequivalence study was done at

Objective: To establish the bioequivalence of three combination analgesic formulations: Excedrin Extra Strength Caplets, Tablets and Geltabs.

Study Design: This was a single-center, open label, single dose, randomized 3-way crossover study. Twenty nine healthy male volunteers between the ages of 18 and 40 years enrolled; however, 28 completed all 3 periods in the study. The subjects were administered a single dose Excedrin ES consisting of either 2 tablets, 2 caplets or 2 geltabs according to a randomized schedule. Each dose was administered after an overnight fast with 240 mL of water. The subjects were not allowed to drink till after 2 hours post each dose and no food was allowed until 4 hours post dose. Ten mL blood samples were collected at predose (0), 20 and 40 mins post dose and then at 1, 1.5, 2, 3.0, 4.0, 6.0, 8.0, 10, and 12 hours post dose.

Dosage Forms: Excedrin ES Tablets (Lot No. 513730) consisted of 250 mg acetylsalicylic acid, 250 mg acetaminophen and 65 mg caffeine. Excedrin ES Caplets (Lot No. 515299) consisted of 250 mg acetylsalicylic acid, 250 mg acetaminophen and 65 mg caffeine and Excedrin ES Geltabs (509136) contained 250 mg acetylsalicylic acid, 250 mg acetaminophen and 65 mg caffeine. The complete composition of the formulations are provided in appendix.

Dosing Regimen:
Treatment 1/B (Reference): Two Excedrin ES tablets administered with 240 mL of water after an over night fast.
Treatment 2/A: Two Excedrin ES Caplets administered with 240 mL of water after an overnight fast.
Treatment 3/C: Two Excedrin ES Geltabs administered with 240 mL of water after an overnight fast.
Each treatment dose was separated by a 6-7 day washout period.

Data Analysis: Pharmacokinetic parameters, Cmax, Tmax, AUC(0-t), AUC(0-∞), AUMC (0-t), AUMC(0-∞), Ke , T½ and MRT were computed using noncompartmental methods. Bioavailability among formulations was assessed for each active ingredient (acetaminophen, caffeine and total salicylate). Separate statistical analysis was conducted for each active ingredient to determine if bioequivalency was achieved.

Results: The plasma concentration profiles of caffeine, total salicylate and acetaminophen were similar after administration of the 3 formulations of Excedrin ES (Figures 1-3).

Fig 1a

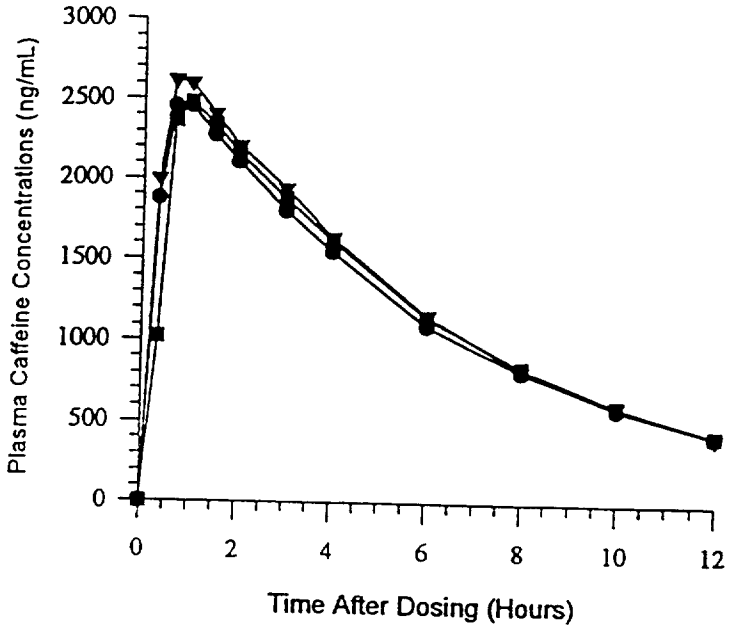

Fig 1b

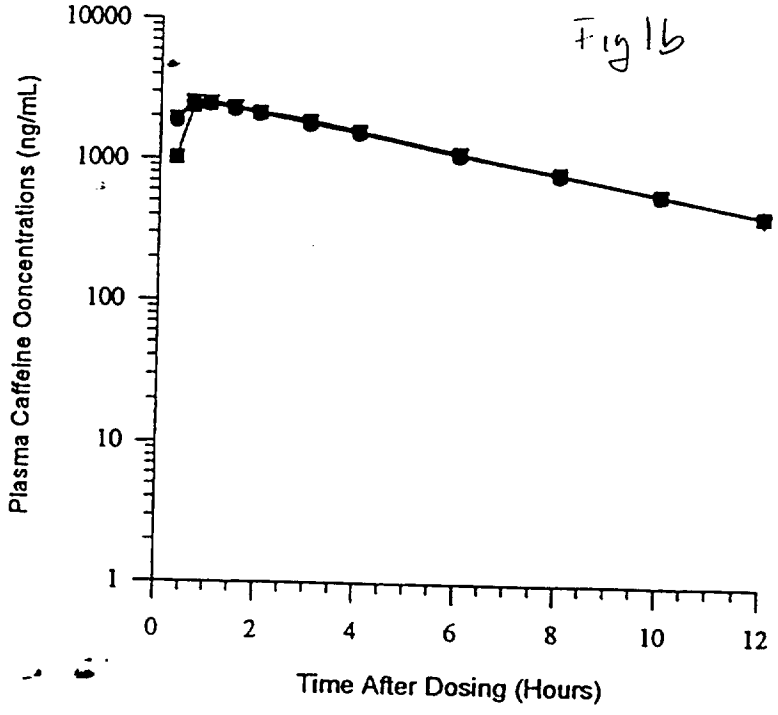

Figure C1. Mean Plasma Caffeine Concentration-Time Profile In Healthy Volunteers

Treatment A — Treatment B — Treatment C

Fig 2a

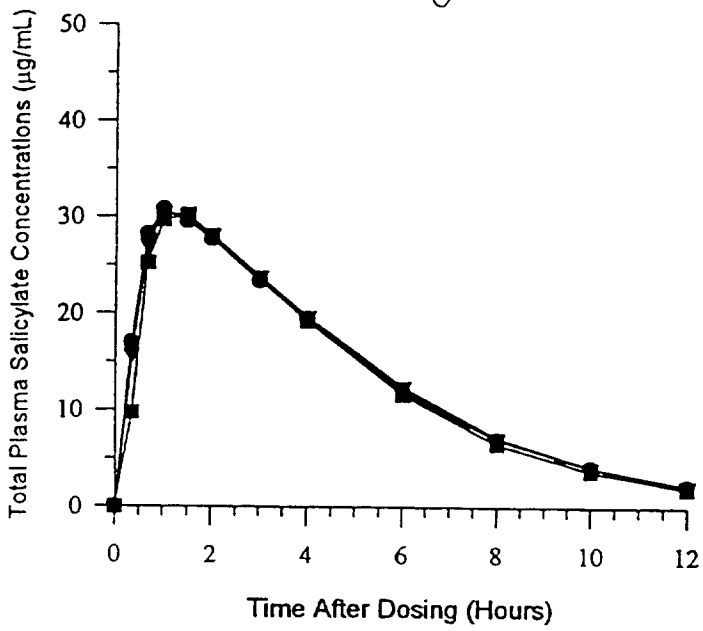

Fig 2b

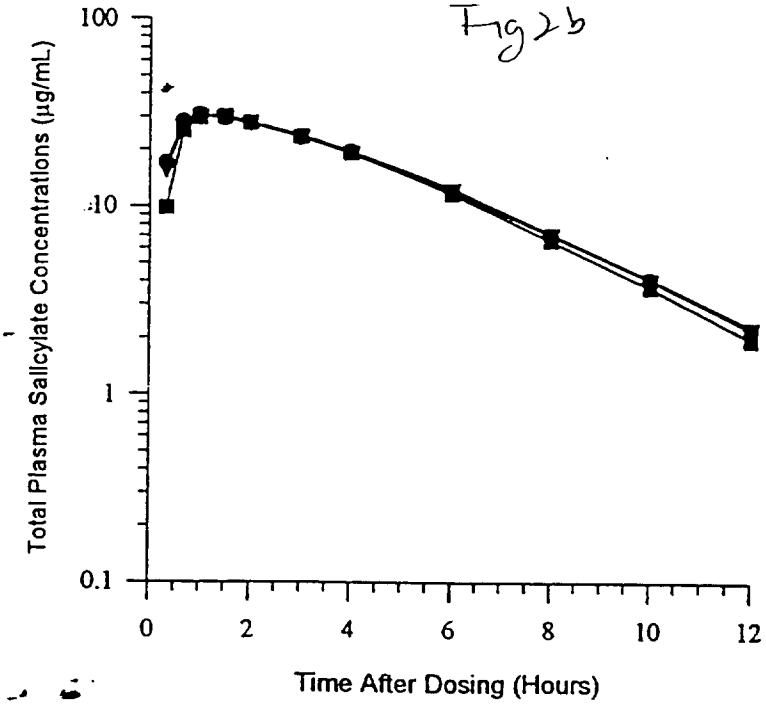

Figure C2. Mean Total Plasma Salicylate Concentration-Time Profile In Healthy Volunteers

Treatment A Treatment B Treatment C

Fig 3a

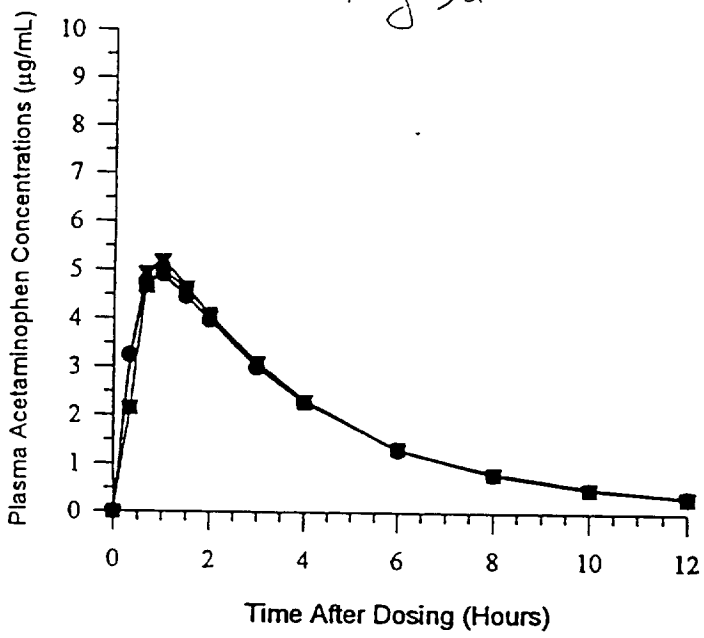

Fig 3b

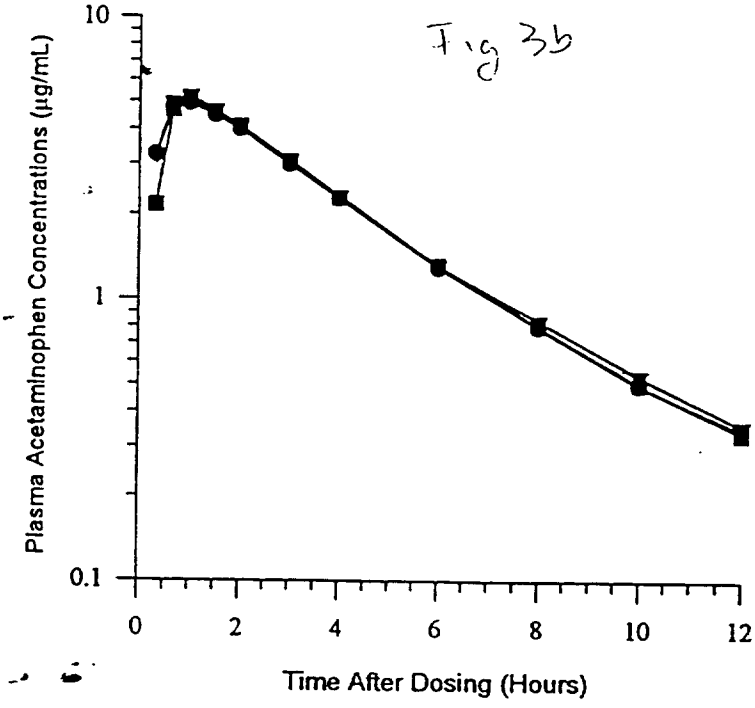

Figure C3. Mean Plasma Acetaminophen Concentration-Time Profile In Healthy Volunteers

Treatment A Treatment B Treatment C

The computed pharmacokinetic parameters for caffeine, total salicylate and acetaminophen are contained in the following Tables.

Summary of Caffeine Pharmacokinetic Parameters After Administration of Excedrin Extra Strength Formulations.

PK Parameters	Tablet	Caplets	Geltabs
		Mean ±SD	
Cmax (ng/mL)	2818±441.8	2640±490.9	2625±390.4
Tmax (hours)	0.70±0.342	0.76±0.31	0.93±0.33
AUC(0-t) (ng*h/mL)	15509±3754.6	14749±3606.4	14889±3496.8
AUC(0-∞) (ng*h/mL)	18466±5739.8	17974±5912.8	17977±5520.0
T ½ (hours)	4.15±1.25	4.36±1.50	4.27±1.35
MRT(po) (hours)	6.24±1.83	6.54±2.16	6.56±1.92

Summary of Total Salicylate Pharmacokinetic Parameters After Administration of Excedrin Extra Strength Formulations.

PK Parameters	Tablets	Caplets	Geltabs
		Mean ±SD	
Cmax (ng/mL)	33.0±6.39	33.6±9.60	32.9±5.21
Tmax (hours)	1.40±0.91	1.44±0.90	1.34±0.61
AUC(0-t) (ng*h/mL)	167±29.4	164±34.4	158±30.4
AUC(0-∞) (ng*h/mL)	176±32.6	174±37.7	166±34.8
T ½ (hours)	2.67±0.44	2.61±0.39	.52±0.44
MRT(po) (hours)	4.52±0.66	4.44±0.71	4.330.70

Summary of Acetaminophen Pharmacokinetic Parameters After Administration of Excedrin Extra Strength Formulations

PK Parameters	Tablets	Caplets	Geltabs
		Mean ±SD	
Cmax (ng/mL)	5.80±1.22	5.48±1.26	5.58±1.05
Tmax (hours)	1.05±0.68	1.00±0.52	0.97±0.47
AUC(0-t) (ng*h/mL)	22.6±4.68	21.8±4.59	21.8±4.59
AUC(0-∞) (ng*h/mL)	24.2±5.32	23.3±5.22	23.2±5.27
T ½ (hours)	2.76±0.37	2.72±0.37	2.68±0.34
MRT(po) (hours)	4.29±0.67	4.26±0.68	4.27±0.67

The pharmacokinetic parameters for caffeine, total salicylate and acetaminophen computed after administration of the Excedrin ES formulations were not significantly different.

The 90% confidence intervals for the log transformed Cmax, AUC(0-t) and AUC(0-∞) are contained in the following tables

Caffeine: 90% Confidence Intervals

Treatment	Ln Cmax	Ln AUC(0-t)	Ln AUC (0-∞)
Caplets vrs Tablets	89.4% - 97.2% (0.93*)	91.4% - 98.2% (0.95*)	92.2% - 101% (0.96*)
Geltabs vrs Tablets	89.4% - 97.2% (0.94*)	92.8% - 99.7% (0.97*)	93.1% - 102% (0.97*)
Geltabs vrs Caplets	96.0% - 104% (1.00*)	97.9% - 105% (0.99*)	96.6% - 105% (1.01*)

(*) Point estimate

Total Salicylate: 90% Confidence Intervals

Treatment	Ln Cmax	Ln AUC(0-t)	Ln AUC (0-∞)
Caplets vrs Tablets	94.5% - 108% (1.01*)	95.0% - 102% (0.98*)	94.6% - 102% (0.98*)
Geltabs vrs Tablets	94.5% - 108% (1.01*)	91.6% - 98.4% (0.95*)	90.7% - 97.8% (0.94*)
Geltabs vrs Caplets	93.7% - 107% (1.00*)	93.0% - 99.9% (0.96*)	93.2% - 98.8% (.96*)

(*) Point estimate

Acetaminophen: 90% Confidence Intervals

Treatment	Ln Cmax	Ln AUC (0-t)	Ln AUC (0-∞)
Caplets vrs Tablets	88.4% - 100% (0.94*)	93.6% - 99.3% (0.96*)	93.4% - 99.2% (0.96*)
Geltabs vrs Tablets	90.9% - 103% (0.96*)	93.3% - 99.1% (0.96*)	92.9% - 98.7% (0.96*)
Geltabs vrs Caplets	96.6% - 109% (1.03*)	96.8% - 103% (1.00*)	96.5% - 103% (0.99*)

(*) Point estimate

The current regulatory requirement for two products to be bioequivalent is for the 90% CI for the products to be contained within 80% and 125%. The 90% CI for Cmax, AUC(0-t) and AUC(0-∞) for caffeine was contained in the regulatory criteria for bioequivalence; however, the 90% CI for Cmax was on the lower side (80% - 100%) of the CI, i.e. the CI did not contain 1. The 90% CI for Cmax, AUC(0-t) and AUC(0-∞) for total salicylate and acetaminophen, when the products are compared, were contained within the regulatory criteria.

Conclusion: The bioavailability of caffeine from the caplets relative to the tablets was 96.4% and for the geltabs relative to the tablets was 97.4%. The bioavailability of total salicylate from the caplets relative to the tablets was 98.3% and for the geltabs relative to the tablets was 94.2%. The bioavailability of acetaminophen from the caplets relative to the tablets was 96.3% and for the geltabs relative to the tablets was 95.8%. The study demonstrated that the 3 formulations were bioequivalent and could be used interchangeably. The applicant stated that no clinically significant adverse events were reported in the study.

GENERAL COMMENTS:

The applicant demonstrated that Excedrin® ES tablets is bioequivalent to the caplets and the geltabs. In the study, the geltabs were also demonstrated to be bioequivalent to the caplets. The dosing regimen the sponsor is recommending, 2 tabs, caplets or geltabs, contains a total of 130 mg of caffeine. During team meetings and discussions, it was noted that the OTC monograph allows 65 mg of caffeine per dose of OTC combination products. The applicant was informed of this during the pre-NDA meeting. This issue is going to be discussed at advisory meeting scheduled for this NDA on 7/15/97.

7/2/97

Kofi A. Kumi, Ph.D.
Pharmacokinetics Reviewer (HFD 880)
Division of Pharmaceutical Evaluation III

Concurrence: 7/14/97

Dennis Bashaw, Pharm.D.
Pharmacokinetics Team Leader
HFD 540/550
Division of Pharmaceutical Evaluation III

CC: NDA 20,802 (original)

HFD-550	Division File
	/PM/SCook
HFD-344	/Viswanathan
HFD-880	/TLDPEIII/Bashaw
	/DPEIII/KKumi
CDR	/DPEIII Drug Files ✓
~~HFD-870~~	(Attn: CDR: B. Murphy) ✓

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pages of trade

secret and/or

confidential

commercial

information

Attachment E: Drug Product Dissolution Testing

Date of Test	Dosage Form and Strength	Lot No./ Batch No.	Dissolution Apparatus	Media, Temp.	Speed of Rotation (rpm)	Collection Times (min)	Units Tested	Range (%) ASA	Range (%) APAP	Range (%) CAFF	Mean % Dissolved (% C.V.) ASA	Mean % Dissolved (% C.V.) APAP	Mean % Dissolved (% C.V.) CAFF
10/22/96	①	51011/513730	2	37.0 °C	100 rpm	5 min	12				91.8%	95.2%	99.2%
"	"	"	2	37.0 °C	100 rpm	15 min	12				100.0%	100.3%	103.2%
"	"	"	2	37.0 °C	100 rpm	30 min	12				100.3%	100.5%	103.1%
"	"	"	2	37.0 °C	100 rpm	45 min	12				100.3%	100.6%	103.0%
"	"	"	2	37.0 °C	100 rpm	60 min	12				100.4%	100.7%	102.8%
10/22/96	②	51012/515299	2	37.0 °C	100 rpm	5 min	12				92.0%	93.6%	96.7%
"	"	"	2	37.0 °C	100 rpm	15 min	12				100.4%	101.2%	102.2%
"	"	"	2	37.0 °C	100 rpm	30 min	12				100.8%	101.5%	102.2%
"	"	"	2	37.0 °C	100 rpm	45 min	12				100.9%	101.7%	102.1%
"	"	"	2	37.0 °C	100 rpm	60 min	12				100.9%	101.7%	101.9%

① Tablet, 250 mg Acetaminophein, 250 mg Aspirin, 65 mgCaffeine per tablet
② Caplet, 250 mg Acetaminophein, 250 mg Aspirin, 65 mgCaffeine per caplet

Attachment E: Drug Product Dissolution Testing (Continued)

Date of Test	Dosage Form and Strength	Lot No./ Batch No.	Dissolution Apparatus	Media, Temp.	Speed of Rotation (rpm)	Collection Times (min)	Units Tested	Range (%) ASA	Range (%) APAP	Range (%) CAFF	Mean % Dissolved (% C.V.) ASA	Mean % Dissolved (% C.V.) APAP	Mean % Dissolved (% C.V.) CAFF
11/05/96	③	⑤	2	37.0 °C	100 rpm	5 min	12				20.8%	35.2%	45.5%
"	"	"	2	37.0 °C	100 rpm	15 min	12				76.2%	85.3%	85.2%
"	"	"	2	37.0 °C	100 rpm	30 min	12				91.8%	98.6%	94.9%
"	"	"	2	37.0 °C	100 rpm	45 min	12				96.0%	102.2%	96.9%
"	"	"	2	37.0 °C	100 rpm	60 min	12				96.4%	102.2%	96.7%
10/22/96	④	40711/40001	2	37.0 °C	100 rpm	5 min	12				91.3%	90.6%	92.3%
"	"	"	2	37.0 °C	100 rpm	15 min	12				96.7%	93.9%	95.4%
"	"	"	2	37.0 °C	100 rpm	30 min	12				96.9%	93.9%	94.1%
"	"	"	2	37.0 °C	100 rpm	45 min	12				96.8%	94.2%	95.0%
"	"	"	2	37.0 °C	100 rpm	60 min	12				96.7%	94.4%	95.0%

③ Geltab, 250 mg Acetaminophein, 250 mg Aspirin, 65 mgCaffeine per caplet
④ Tablet, 250 mg Acetaminophein, 250 mg Aspirin, 65 mgCaffeine per tablet
⑤ Lot No. 50612, Batch No. 509136, Inhouse Lot No. 9503985 (after return from)

Attachment D: In Vivo Analytical Methods Summary

	Type of Biological Fluid	Analytes	Method	Sensitivity	Range	Comments
Study CRP 116-01-95						
Aspirin	Plasma	Total Salicylate	HPLC	0.250 µg/mL		
Acetaminophen	Plasma	Acetaminophen	HPLC	0.20 µg/mL		
Caffeine	Plasma	Caffeine	HPLC	50 ng/mL		