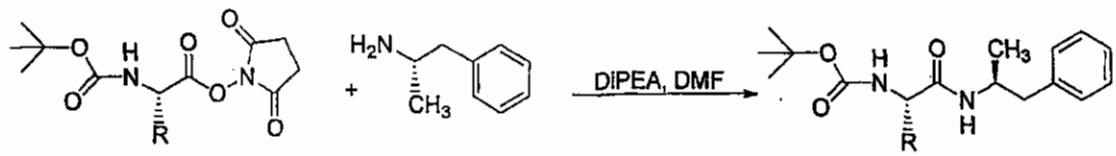
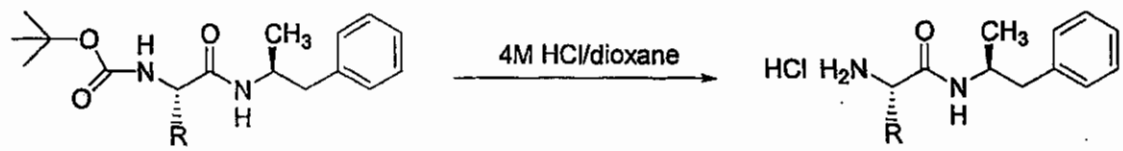
Figure 1



Step 1: Coupling



Step 2: Deprotection

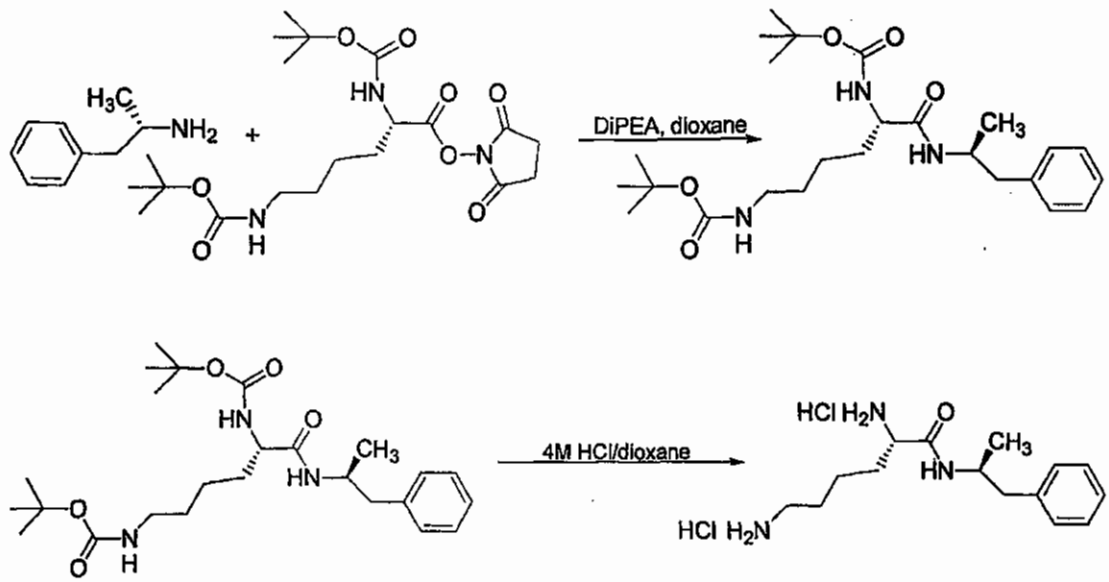


Figure 2

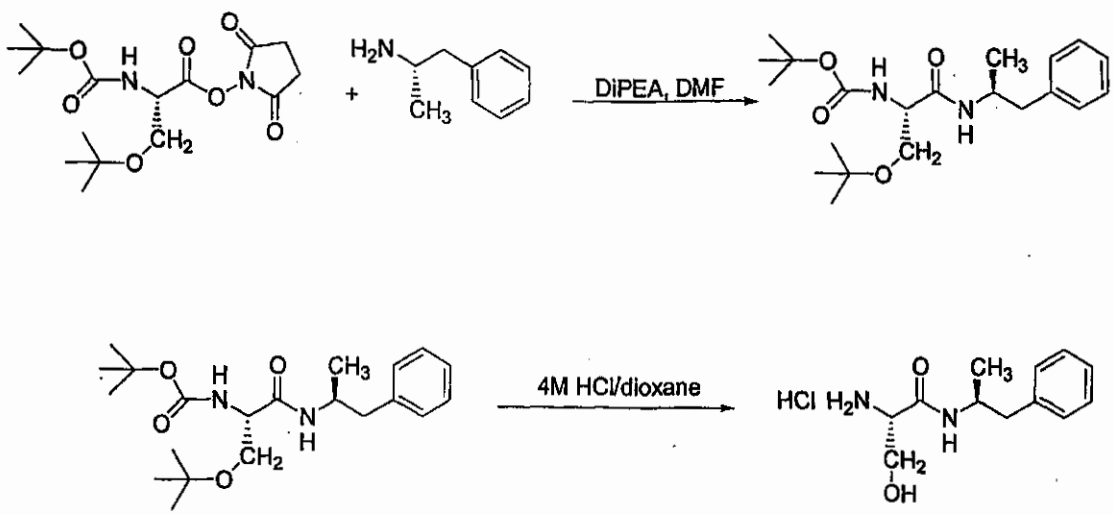


Figure 3

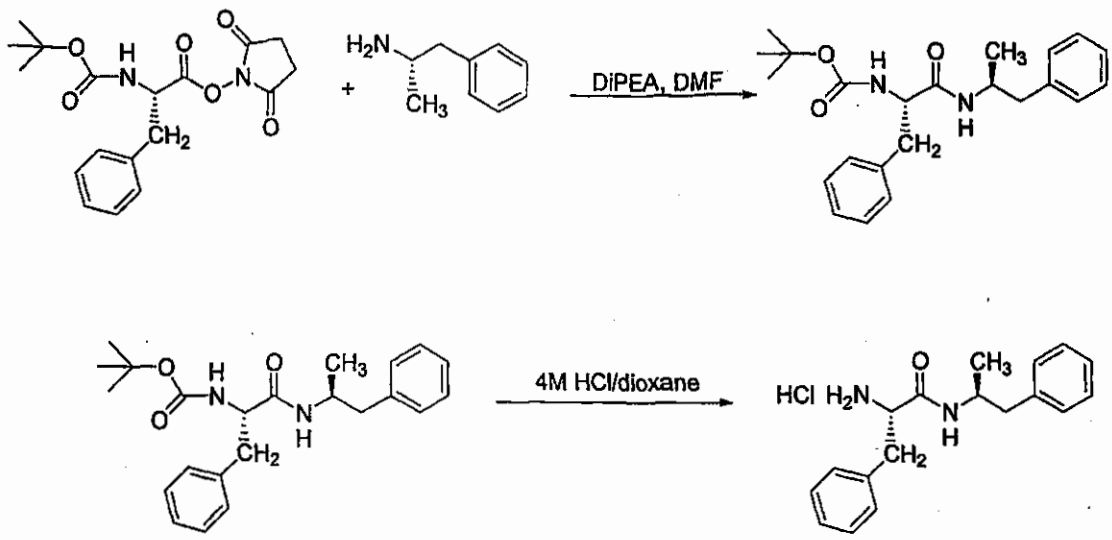


Figure 4

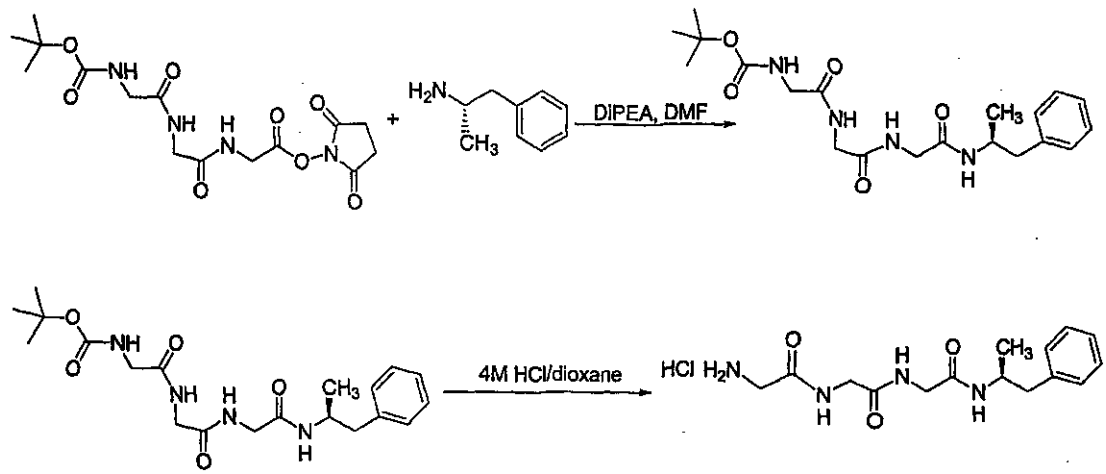


Figure 5

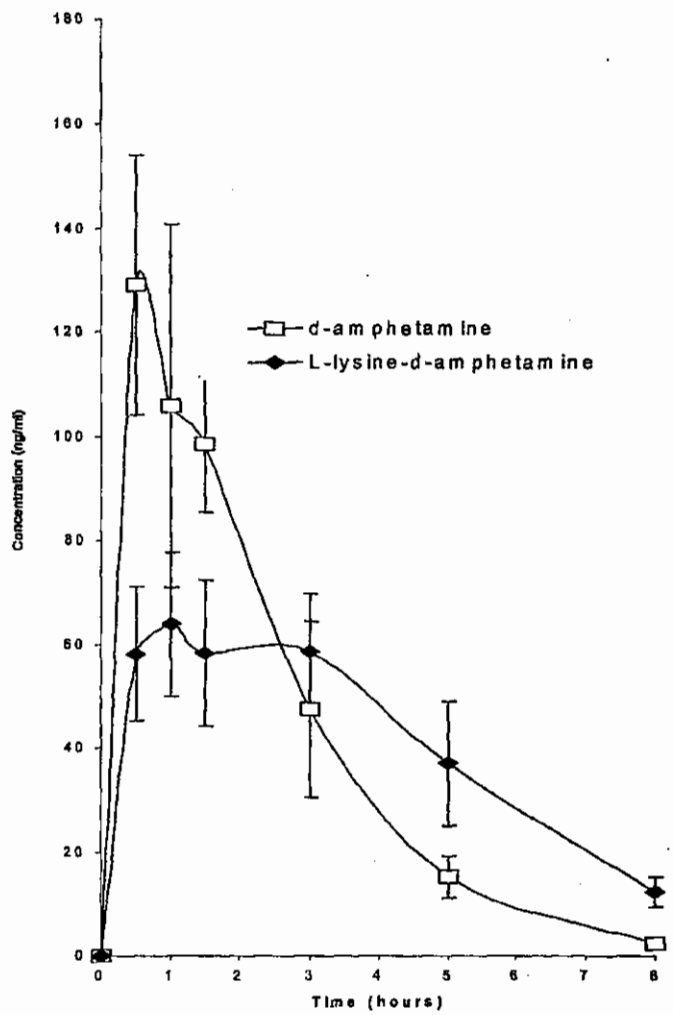

180
160
140
120
100
80
60
40
20
0
Concentration (ng/ml)
0
1
2
3
4
5
6
7
8
Time (hours)
d-amphetamine
L-lysine-d-amphetamine

Figure 6

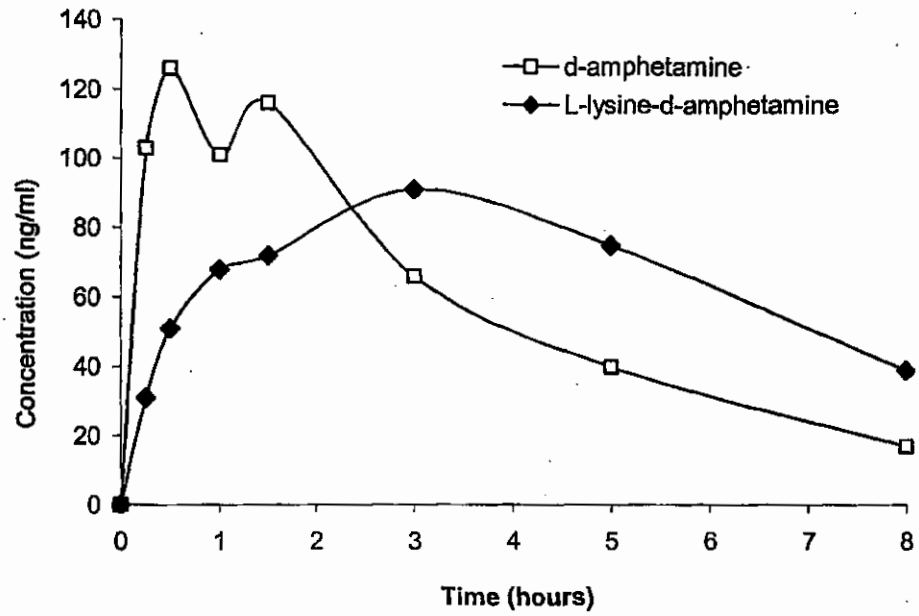

140
120
100
80
60
40
20
0
Concentration (ng/ml)
0
1
2
3
4
5
6
7
8
Time (hours)
d-amphetamine
L-lysine-d-amphetamine

Figure 7

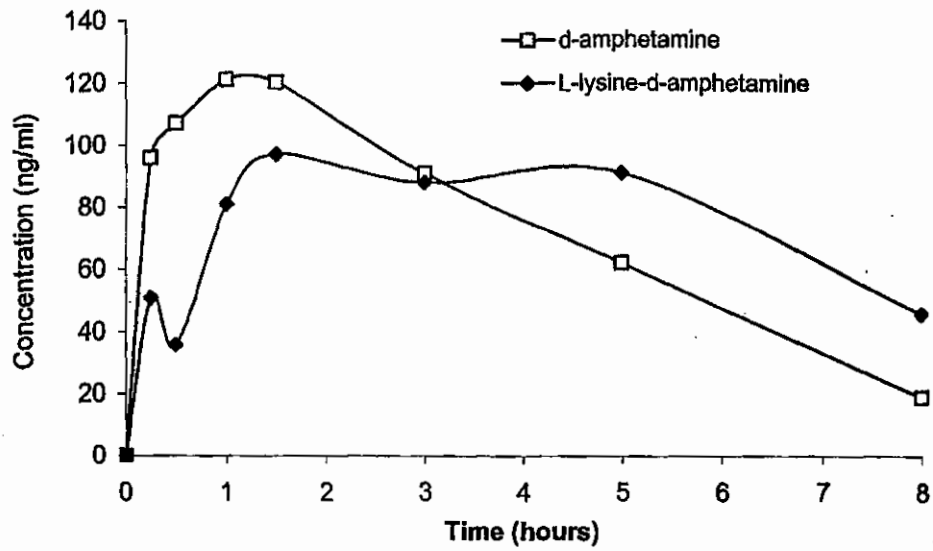

140
120
100
80
60
40
20
0
Concentration (ng/ml)
0
1
2
3
4
5
6
7
8
Time (hours)
d-amphetamine
L-lysine-d-amphetamine

Figure 8

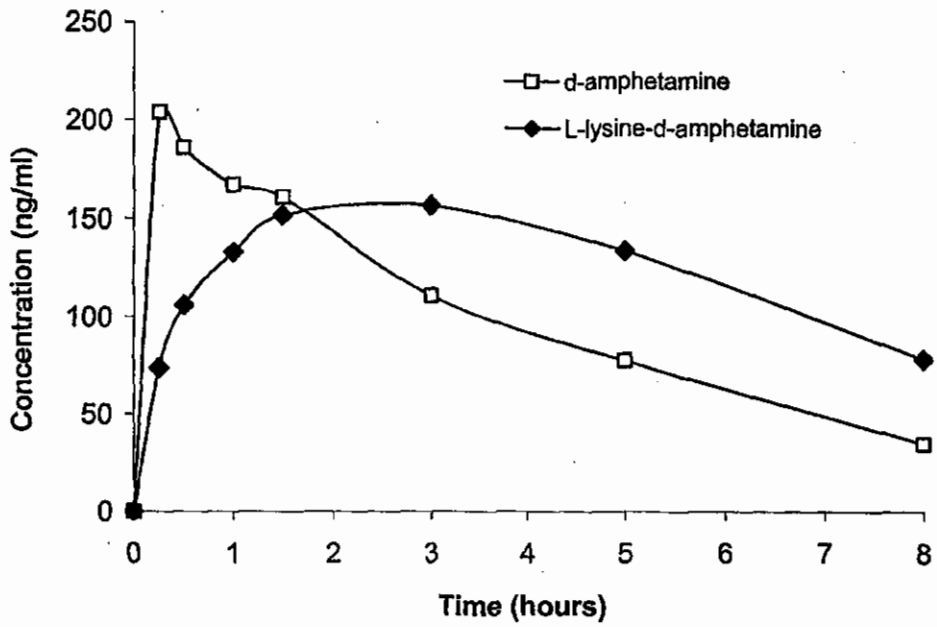

250
200
150
100
50
0
Concentration (ng/ml)
d-amphetamine
L-lysine-d-amphetamine
0
1
2
3
4
5
6
7
8
Time (hours)

Figure 9

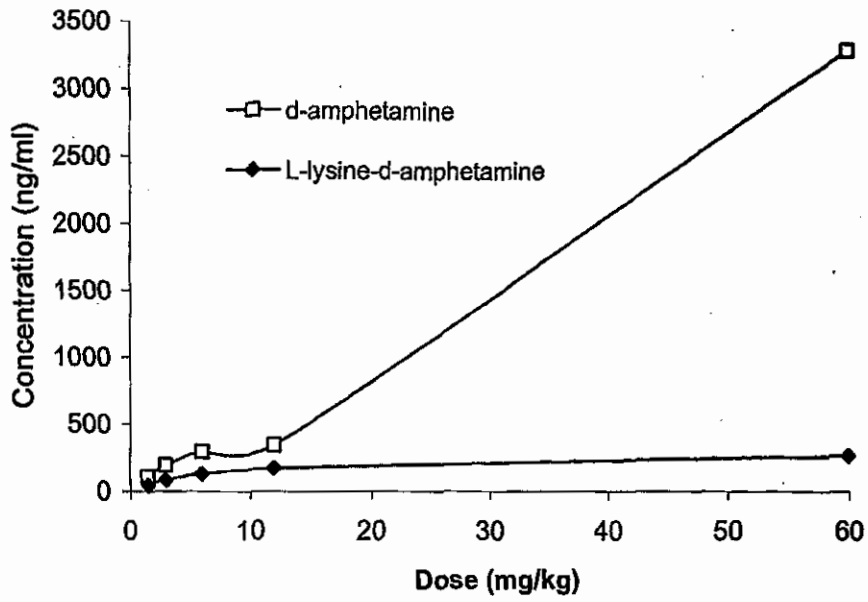

3500
3000
2500
2000
1500
1000
500
0
Concentration (ng/ml)
d-amphetamine
L-lysine-d-amphetamine
0
10
20
30
40
50
60
Dose (mg/kg)

Figure 10

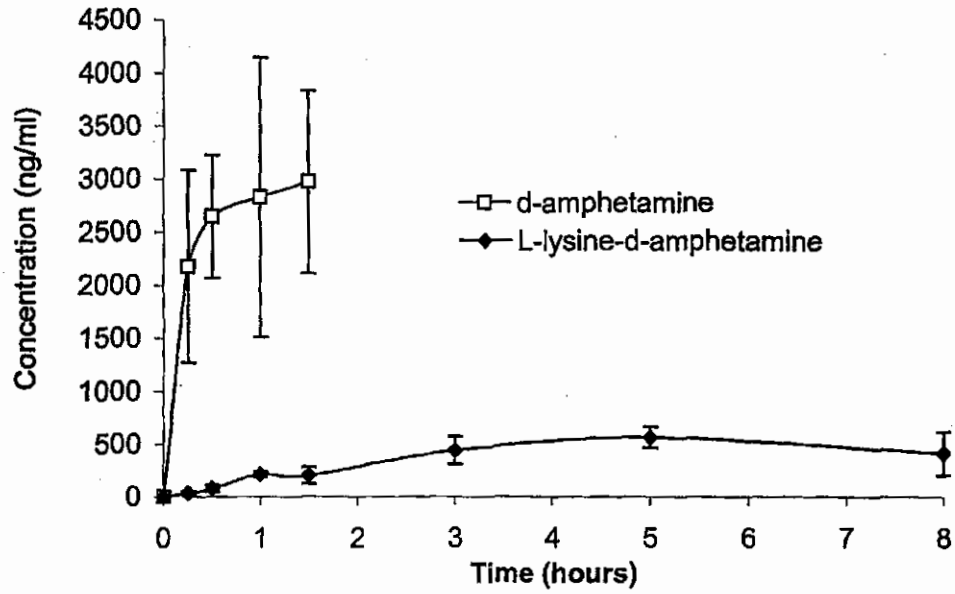

4500
4000
3500
3000
2500
2000
1500
1000
500
0
Concentration (ng/ml)
0
1
2
3
4
5
6
7
8
Time (hours)
d-amphetamine
L-lysine-d-amphetamine

Figure 11

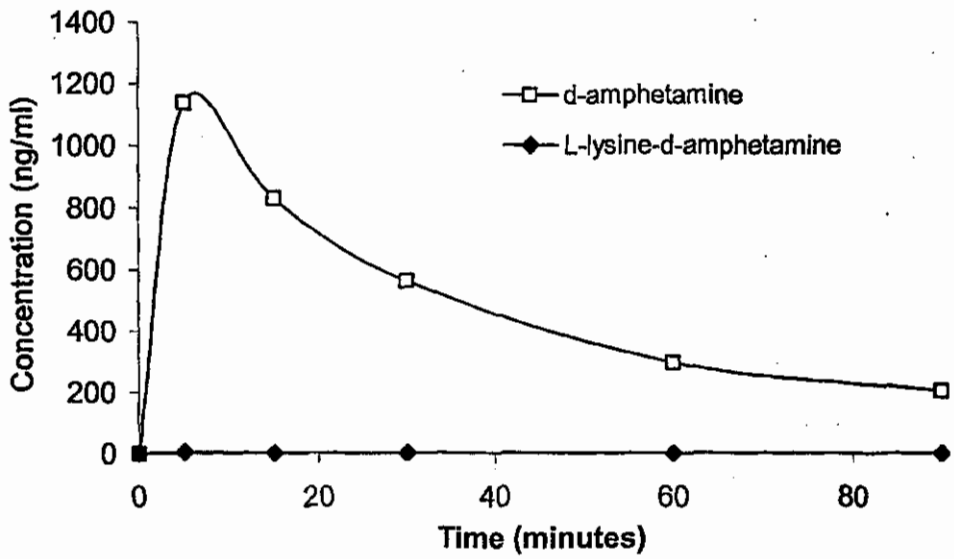

1400
1200
1000
800
600
400
200
0
Concentration (ng/ml)
0
20
40
60
80
Time (minutes)
d-amphetamine
L-lysine-d-amphetamine

Figure 12

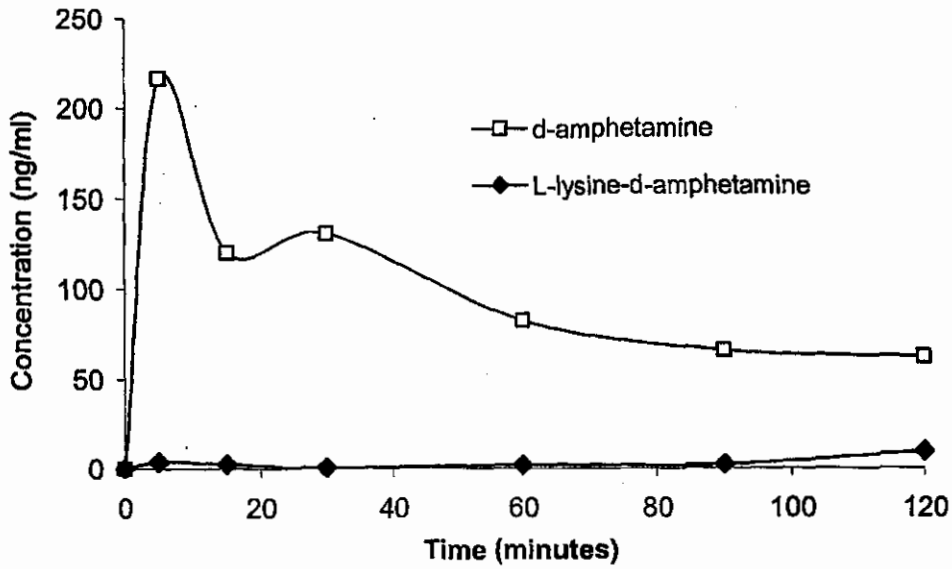

250
200
150
100
50
0
Concentration (ng/ml)
d-amphetamine
L-lysine-d-amphetamine
0
20
40
60
80
100
120
Time (minutes)

Figure 13

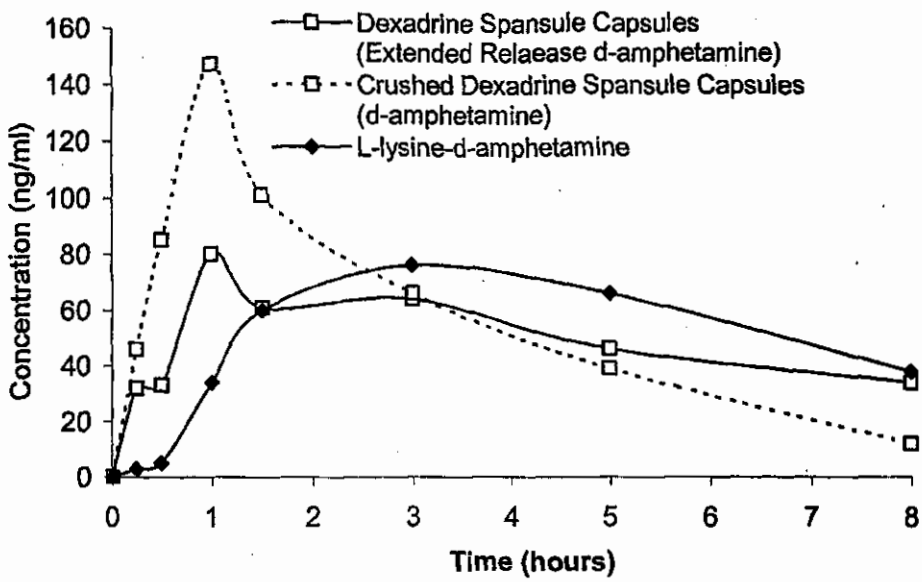

Dexadrine Spansule Capsules
(Extended Relaease d-amphetamine)
Crushed Dexadrine Spansule Capsules
(d-amphetamine)
L-lysine-d-amphetamine
Concentration (ng/ml)
160
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
Time (hours)

Figure 14

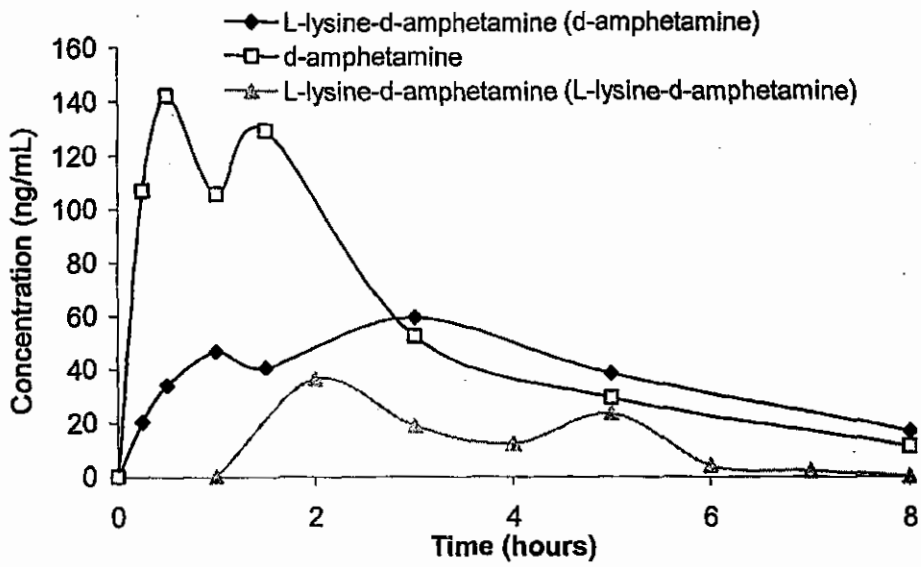


Figure 15A

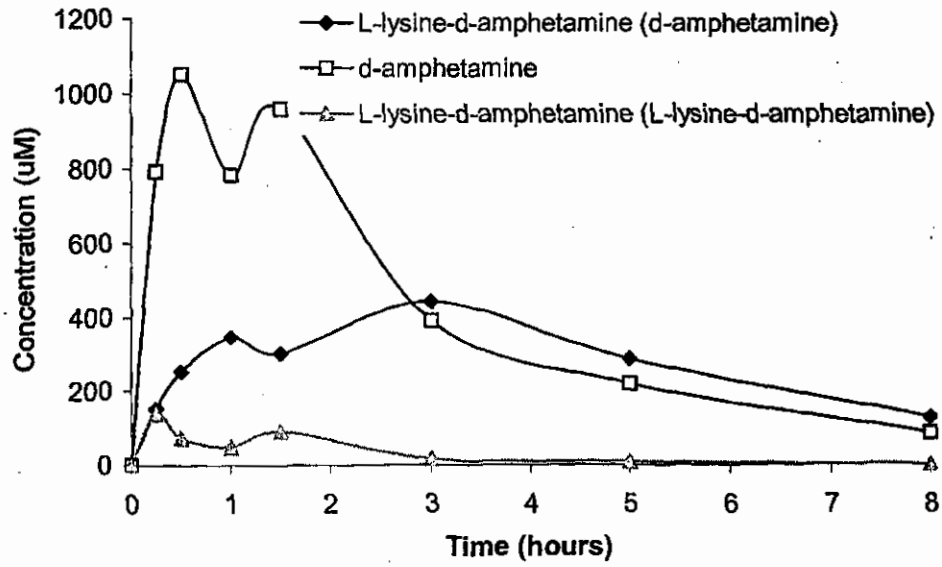


Figure 15B

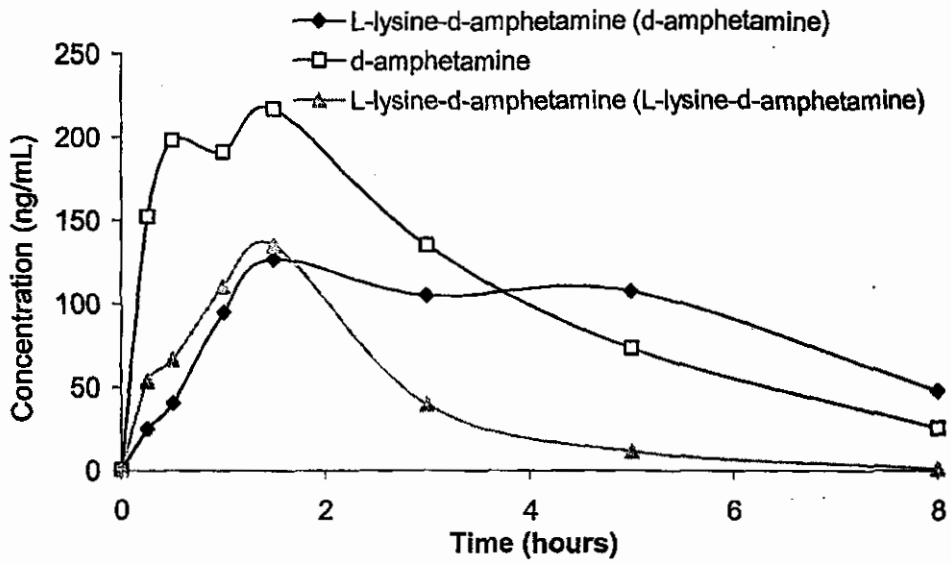


Figure 16A

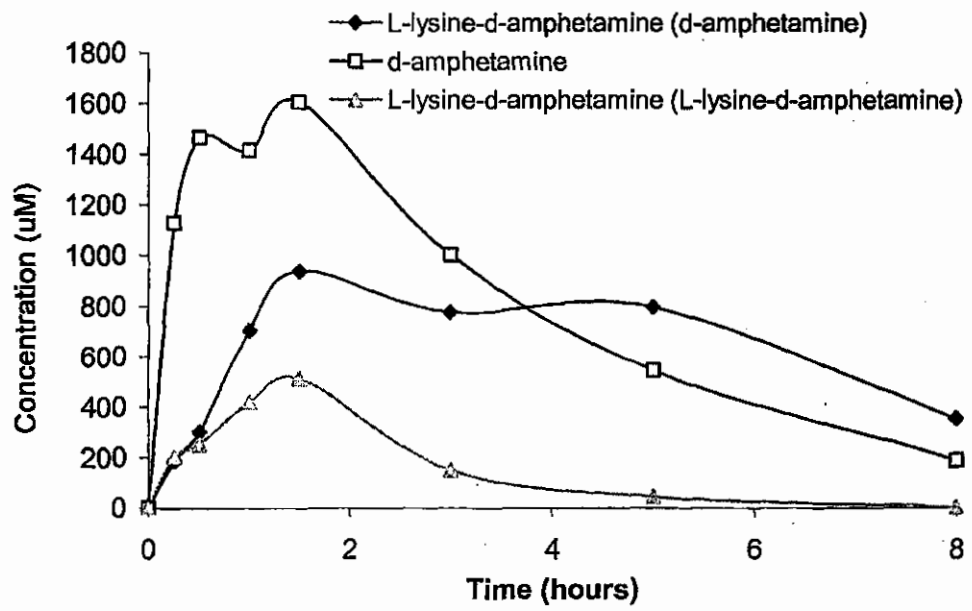


Figure 16B

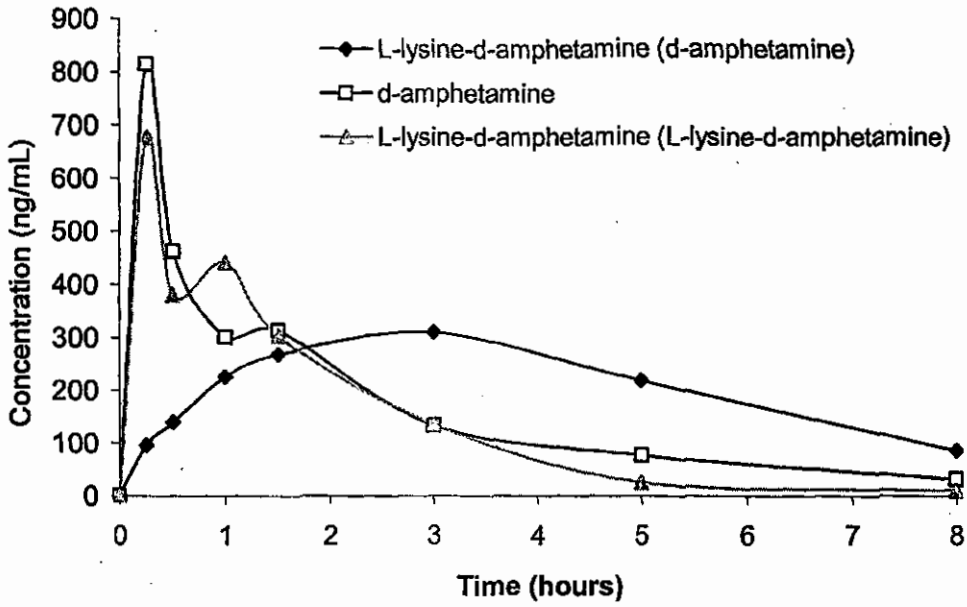


Figure 17A

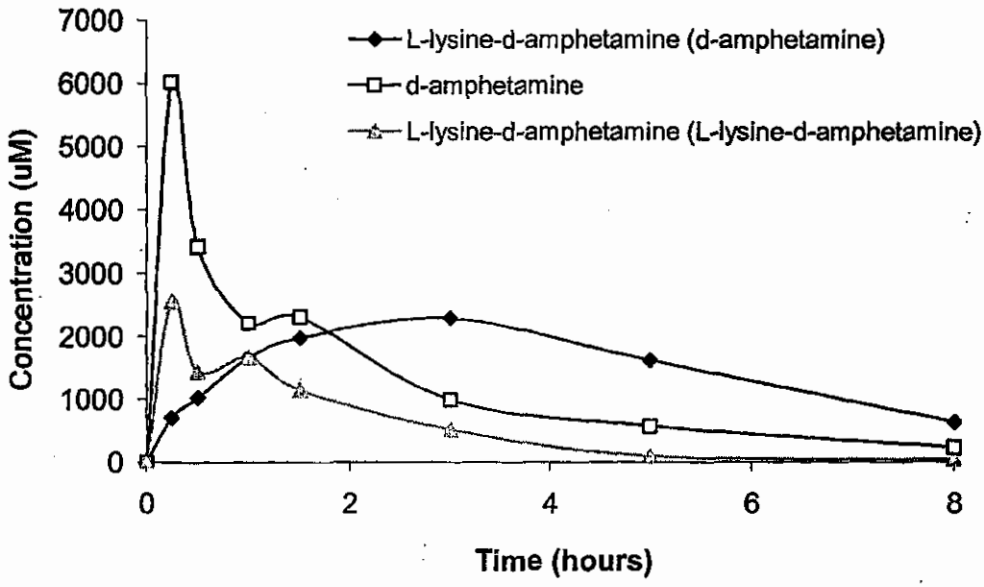


Figure 17B

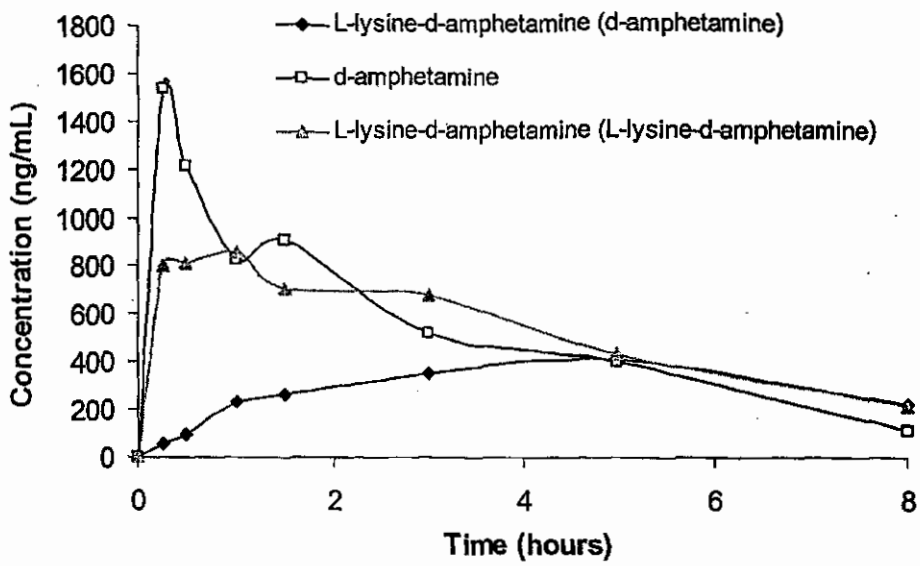


Figure 18A

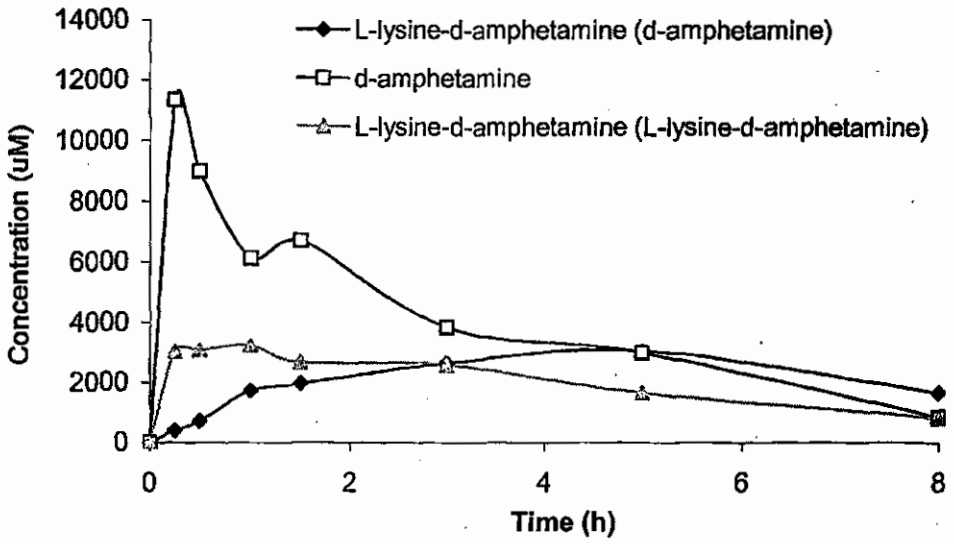


Figure 18B

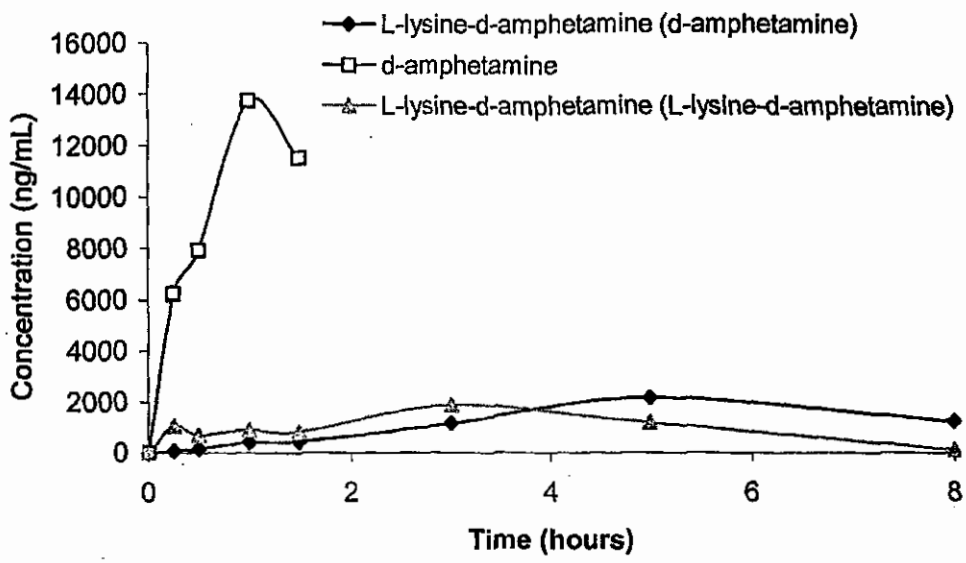


Figure 19A

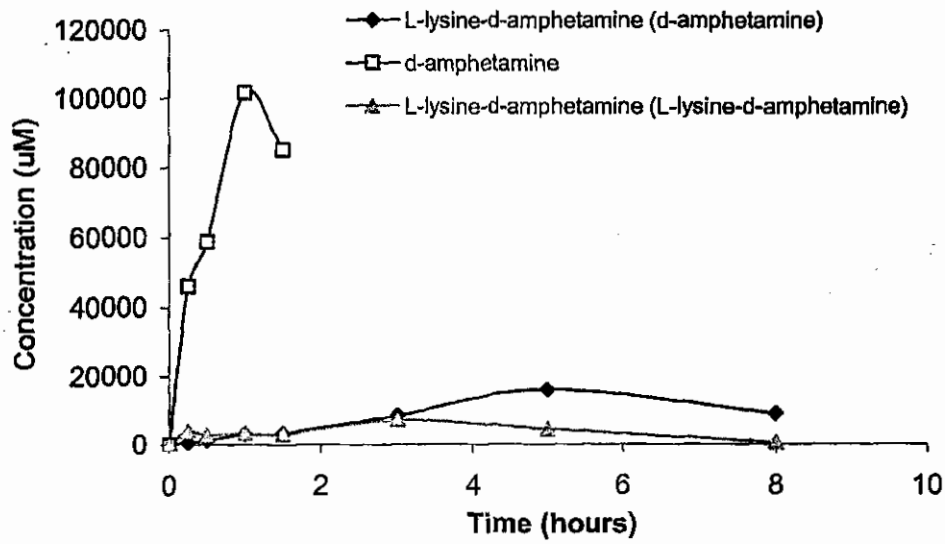


Figure 19B

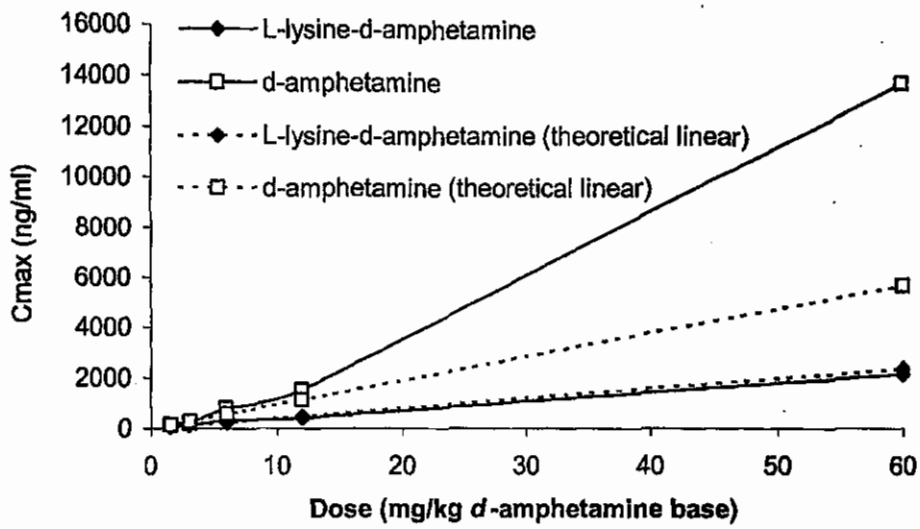

16000
14000
12000
10000
8000
6000
4000
2000
0
Cmax (ng/ml)
L-lysine-d-amphetamine
d-amphetamine
L-lysine-d-amphetamine (theoretical linear)
d-amphetamine (theoretical linear)
0
10
20
30
40
50
60
Dose (mg/kg d-amphetamine base)

Figure 20

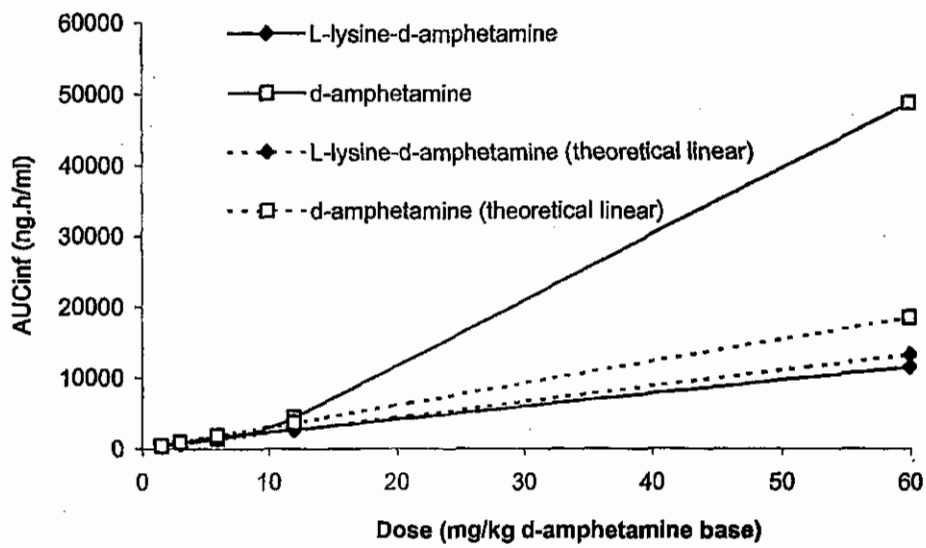

60000
50000
40000
30000
20000
10000
0
AUCinf (ng.h/ml)
L-lysine-d-amphetamine
d-amphetamine
L-lysine-d-amphetamine (theoretical linear)
d-amphetamine (theoretical linear)
0
10
20
30
40
50
60
Dose (mg/kg d-amphetamine base)

Figure 21

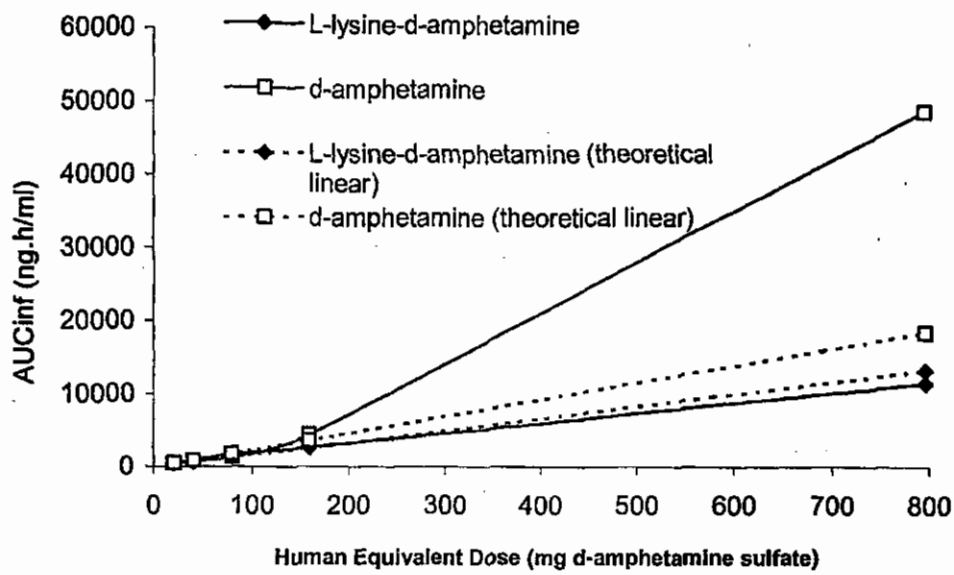

60000
50000
40000
30000
20000
10000
0
AUCinf (ng.h/ml)
L-lysine-d-amphetamine
d-amphetamine
L-lysine-d-amphetamine (theoretical linear)
d-amphetamine (theoretical linear)
0
100
200
300
400
500
600
700
800
Human Equivalent Dose (mg d-amphetamine sulfate)

Figure 22

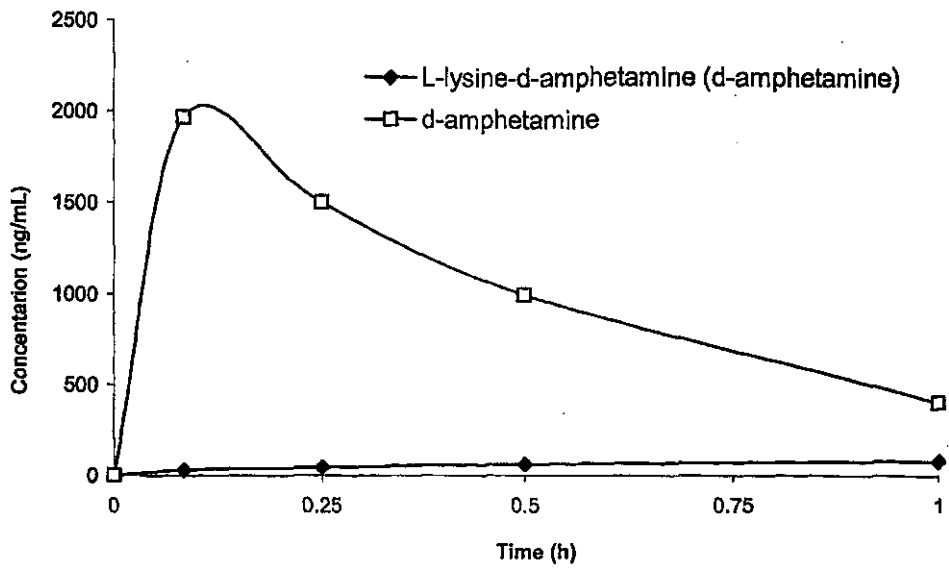

2500
2000
1500
1000
500
0
Concentarion (ng/mL)
L-lysine-d-amphetamine (d-amphetamine)
d-amphetamine
0
0.25
0.5
0.75
1
Time (h)

Figure 23

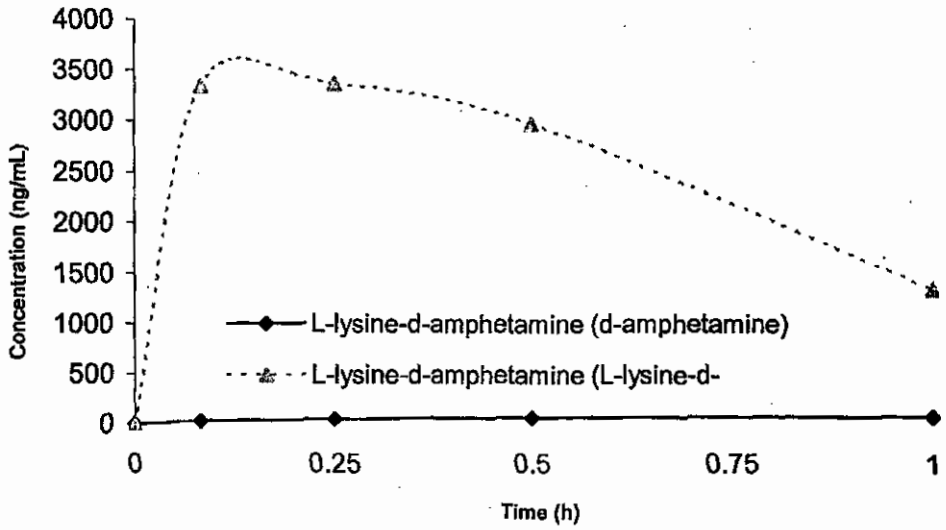


Figure 24A

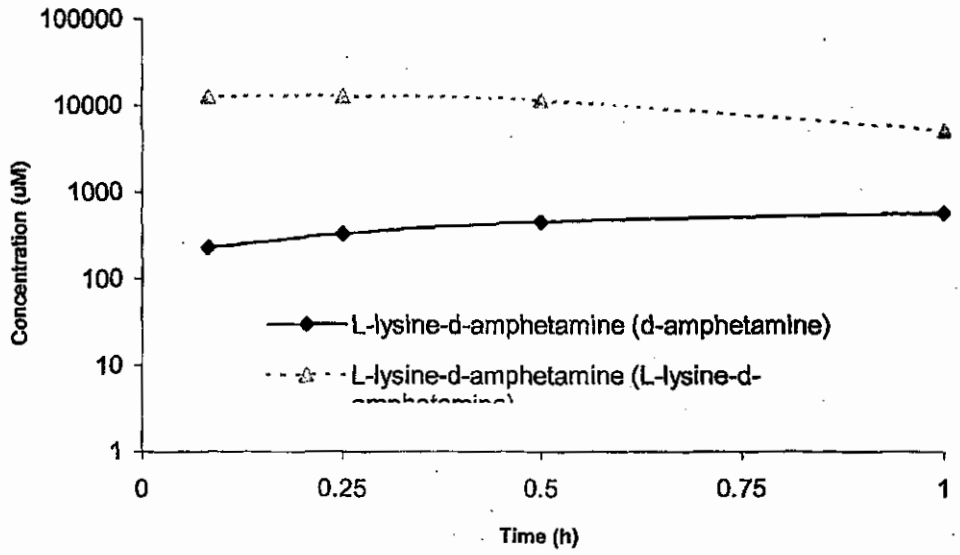


Figure 24B

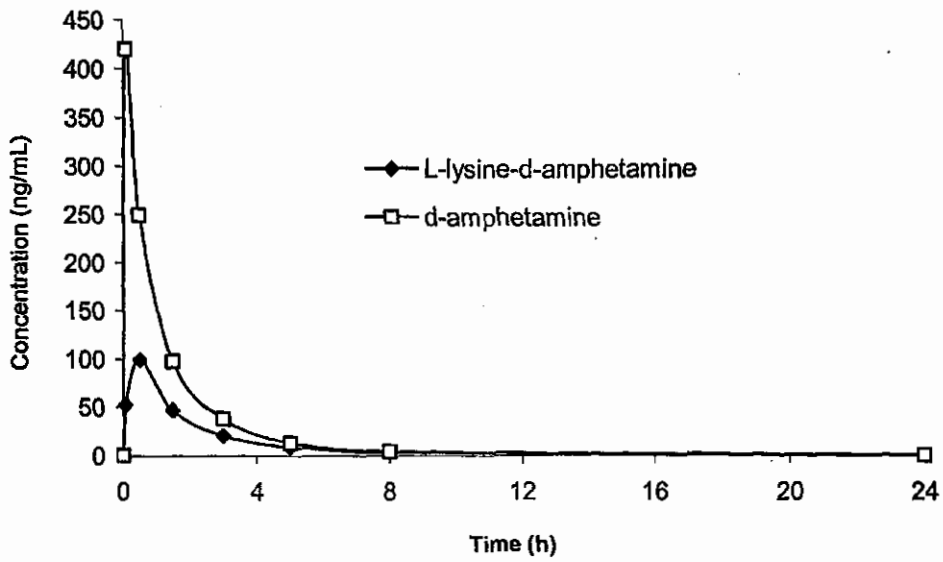

450
400
350
300
250
200
150
100
50
0
Concentration (ng/mL)
0
4
8
12
16
20
24
Time (h)
L-lysine-d-amphetamine
d-amphetamine

Figure 25

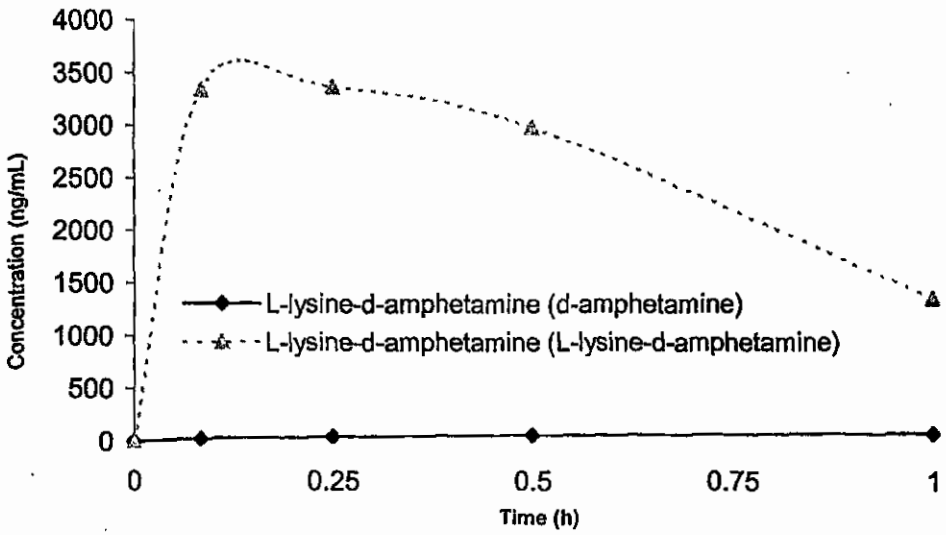


Figure 26A

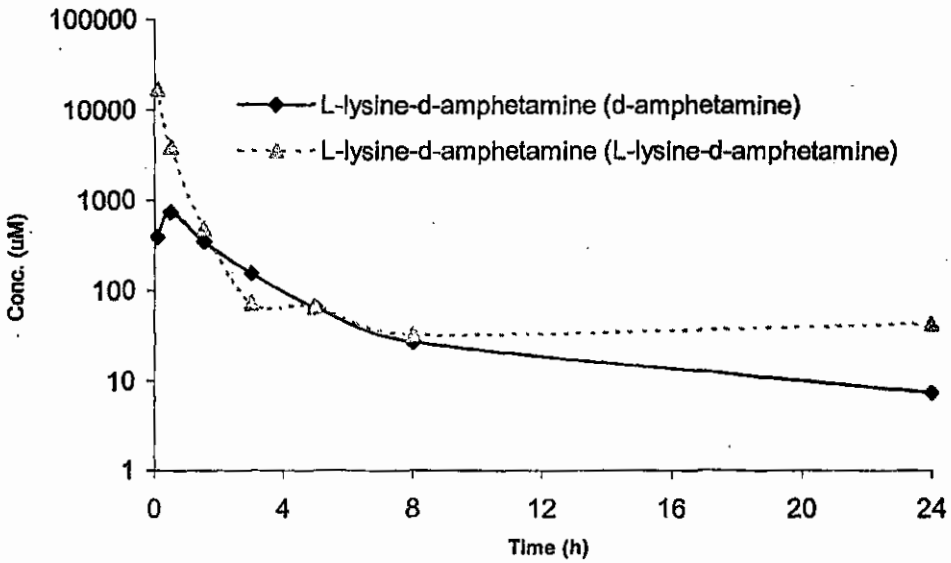


Figure 26B

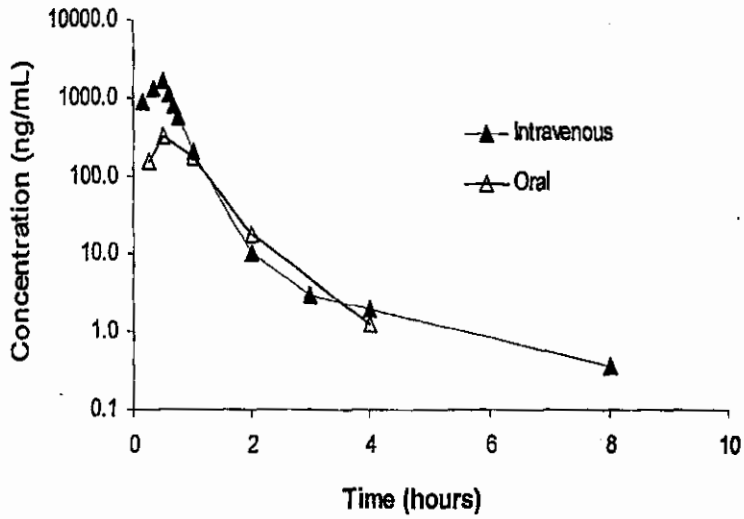

10000.0
1000.0
100.0
10.0
1.0
0.1
Concentration (ng/mL)
0
2
4
6
8
10
Time (hours)
Intravenous
Oral

Figure 27

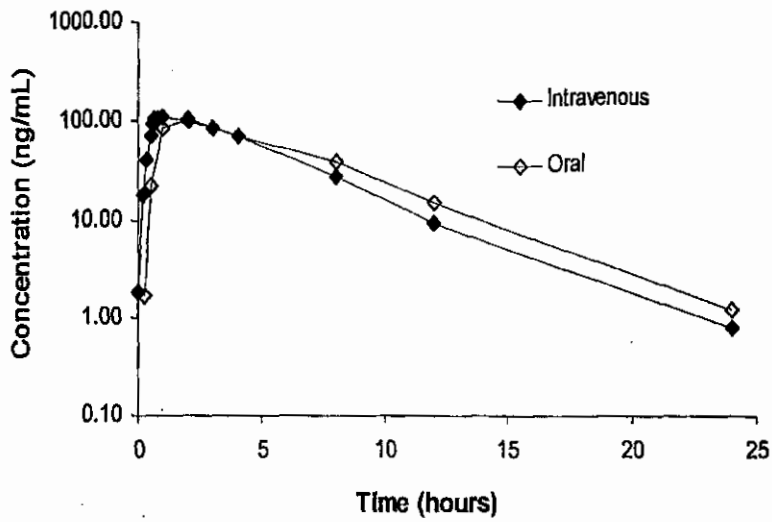

1000.00
100.00
10.00
1.00
0.10
Concentration (ng/mL)
0
5
10
15
20
25
Time (hours)
Intravenous
Oral

Figure 28

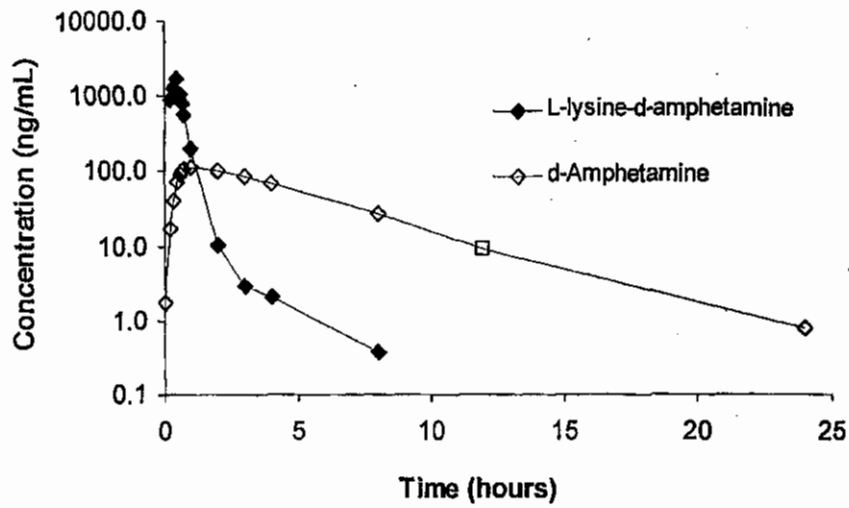


Figure 29A

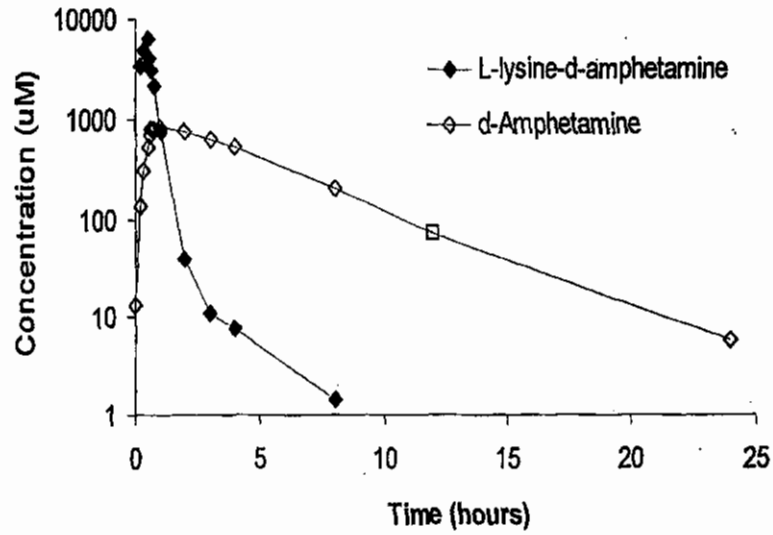


Figure 29B

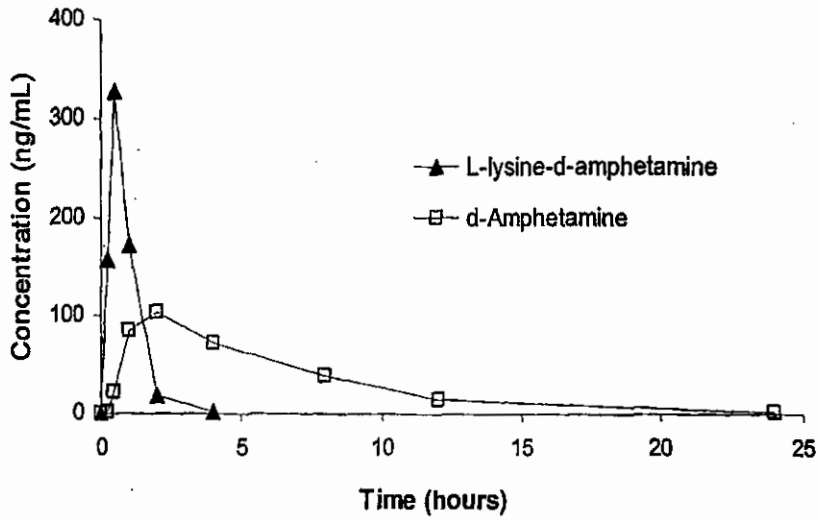


Figure 30A

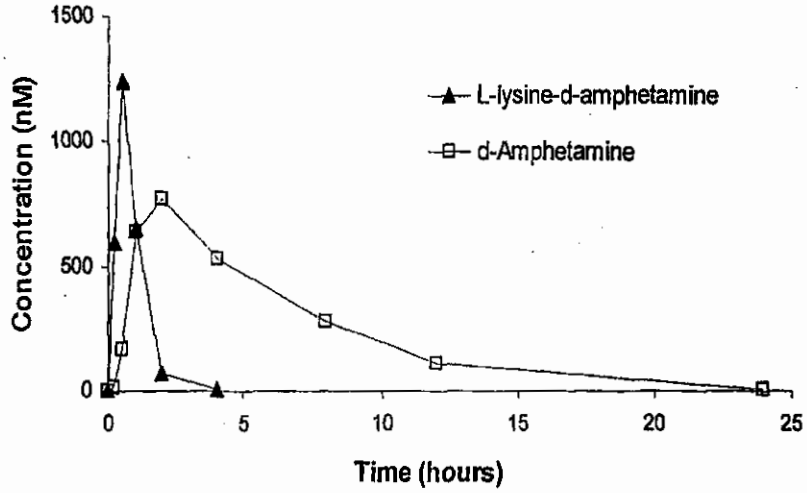


Figure 30B

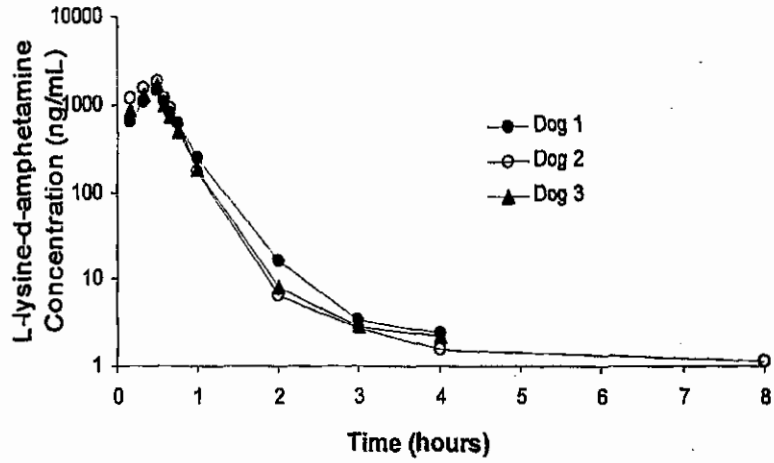


Figure 31A

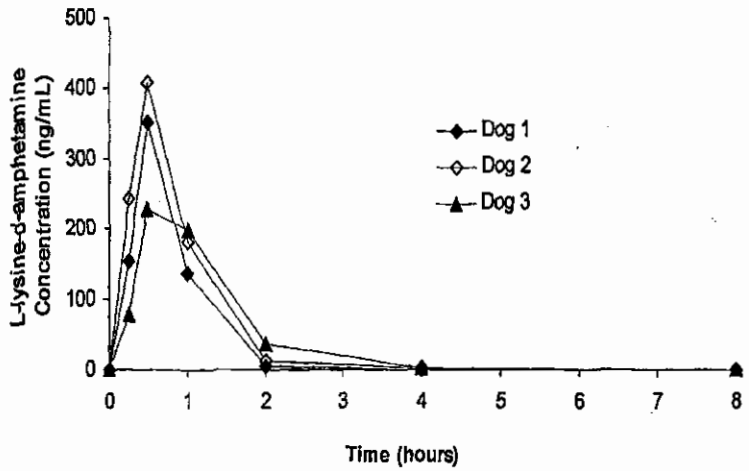


Figure 31B

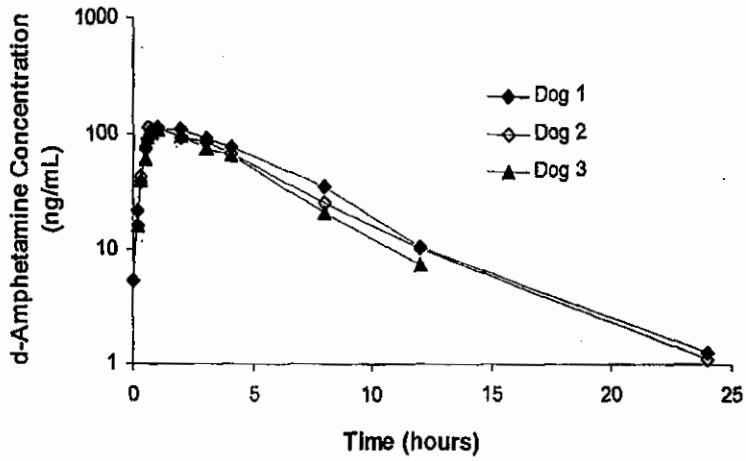


Figure 32A

Oral Formulation: Solution, 0 2 mg/mL in water

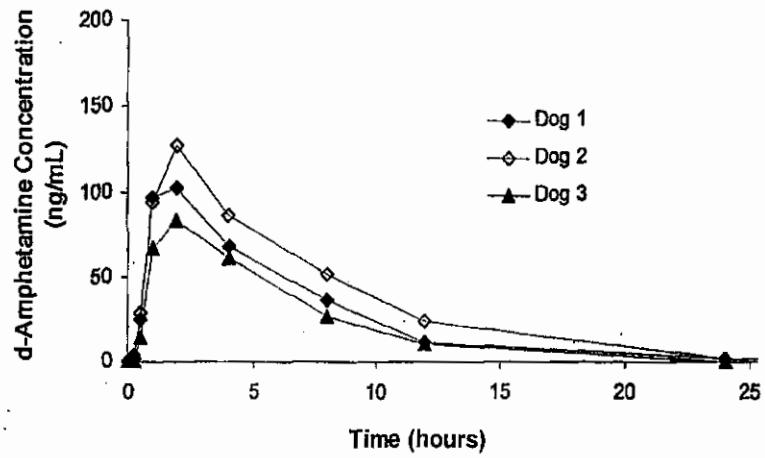


Figure 32B

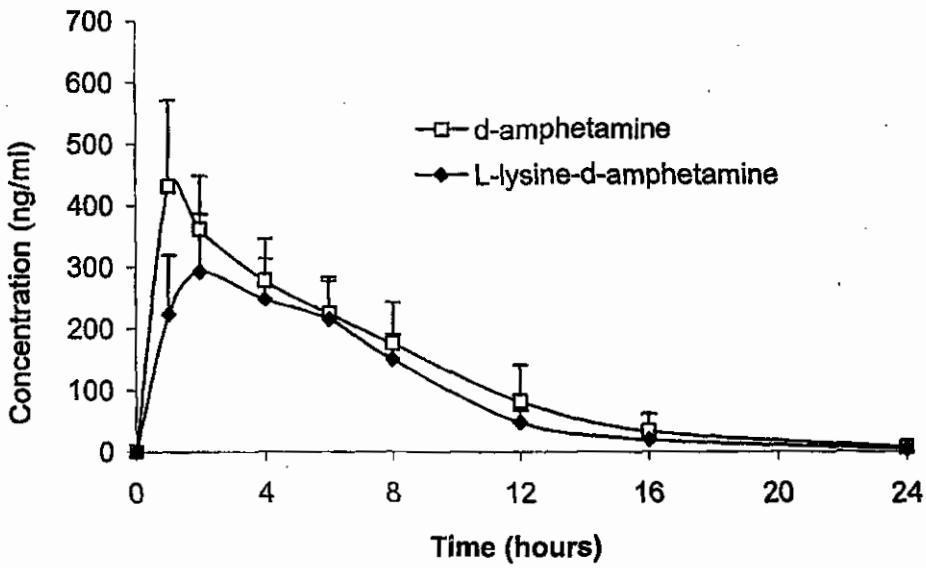

700
600
500
400
300
200
100
0
Concentration (ng/ml)
d-amphetamine
L-lysine-d-amphetamine
0
4
8
12
16
20
24
Time (hours)

Figure 33

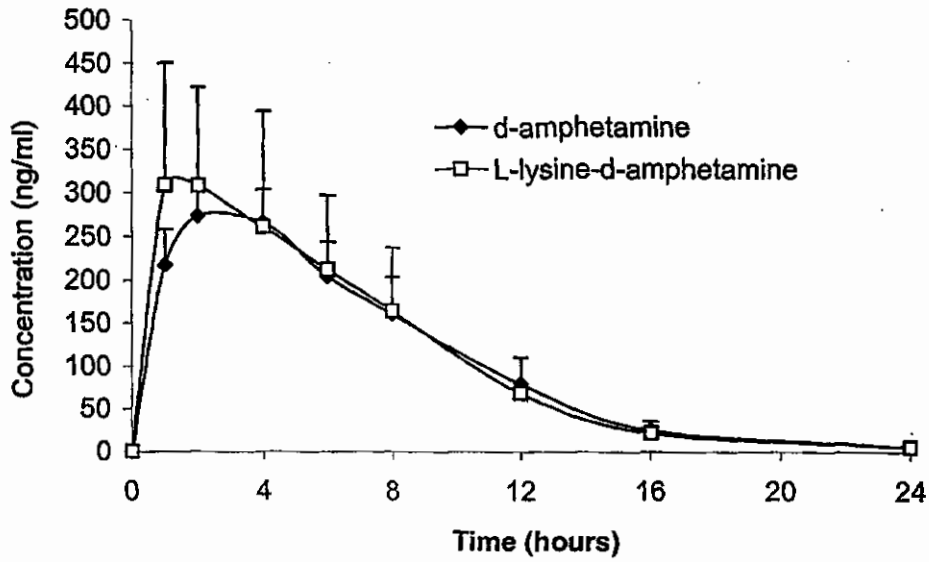

500
450
400
350
300
250
200
150
100
50
0
Concentration (ng/ml)
d-amphetamine
L-lysine-d-amphetamine
0
4
8
12
16
20
24
Time (hours)

Figure 34

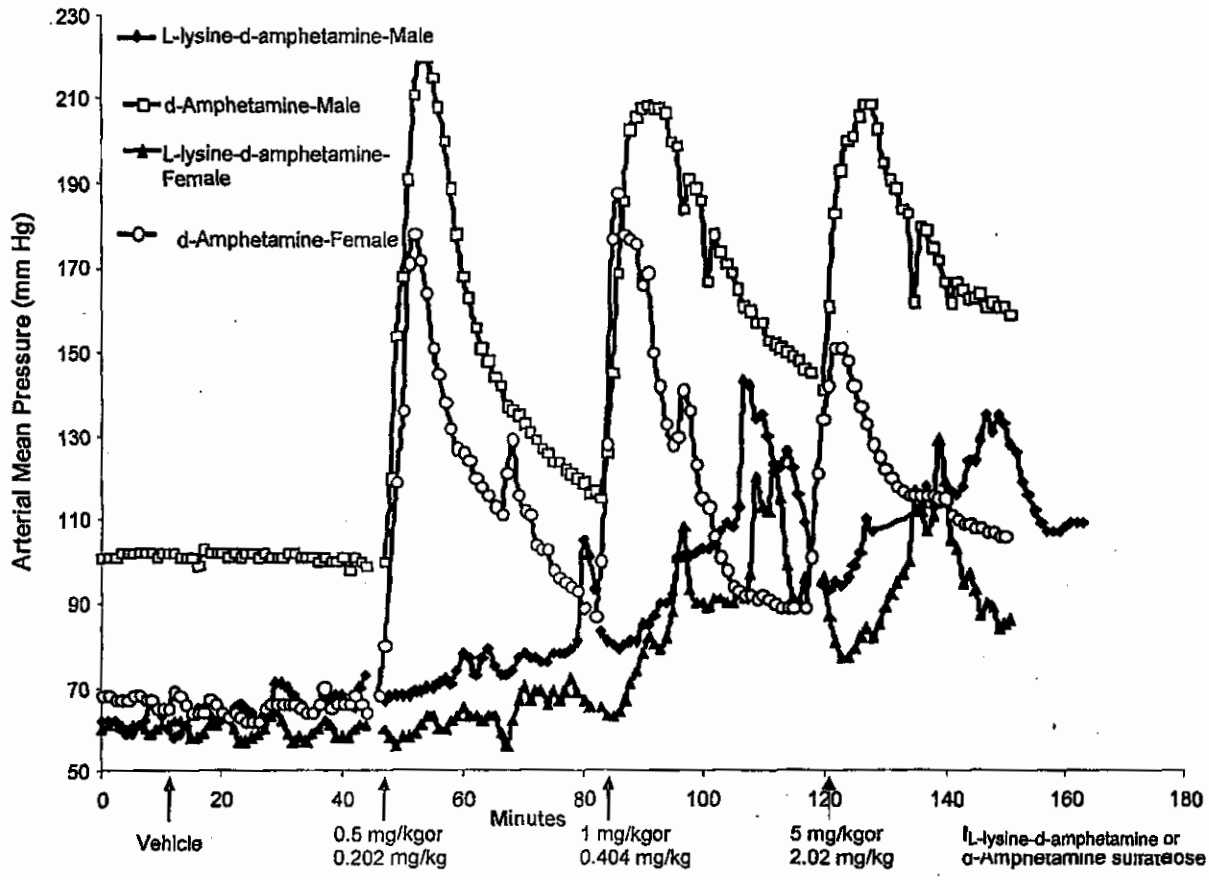

L-lysine-d-amphetamine-Male
d-Amphetamine-Male
L-lysine-d-amphetamine-Female
d-Amphetamine-Female
Arterial Mean Pressure (mm Hg)
230
210
190
170
150
130
110
90
70
50
0
20
40
60
80
100
120
140
160
180
Minutes
Vehicle
0.5 mg/kgor 0.202 mg/kg
1 mg/kgor 0.404 mg/kg
5 mg/kgor 2.02 mg/kg
L-lysine-d-amphetamine or d-Ampnetamine sulfate

Figure 35

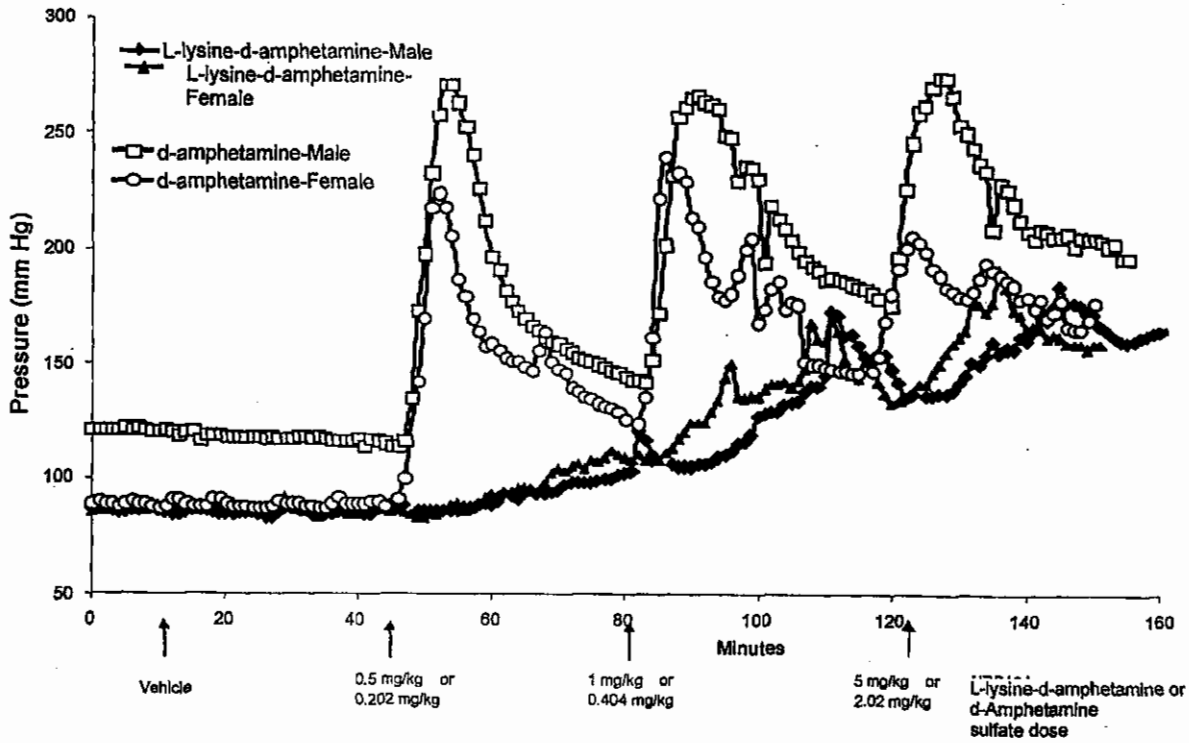

L-lysine-d-amphetamine-Male
L-lysine-d-amphetamine-Female
d-amphetamine-Male
d-amphetamine-Female
Pressure (mm Hg)
300
250
200
150
100
50
0
20
40
60
80
100
120
140
160
Minutes
Vehicle
0.5 mg/kg or 0.202 mg/kg
1 mg/kg or 0.404 mg/kg
5 mg/kg or 2.02 mg/kg
L-lysine-d-amphetamine or d-Amphetamine sulfate dose

Figure 36

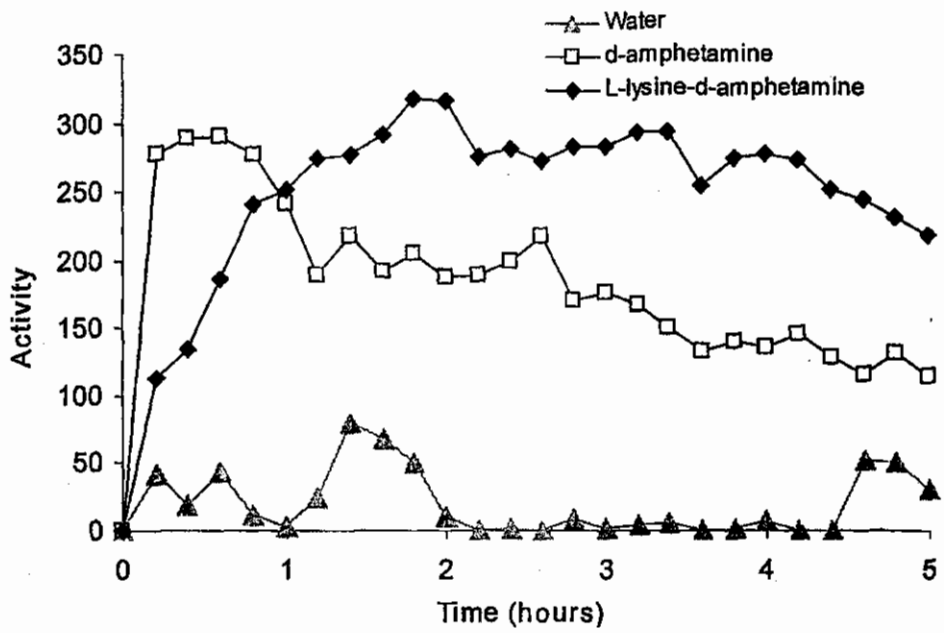

Water
d-amphetamine
L-lysine-d-amphetamine
Activity
350
300
250
200
150
100
50
0
0
1
2
3
4
5
Time (hours)

Figure 37

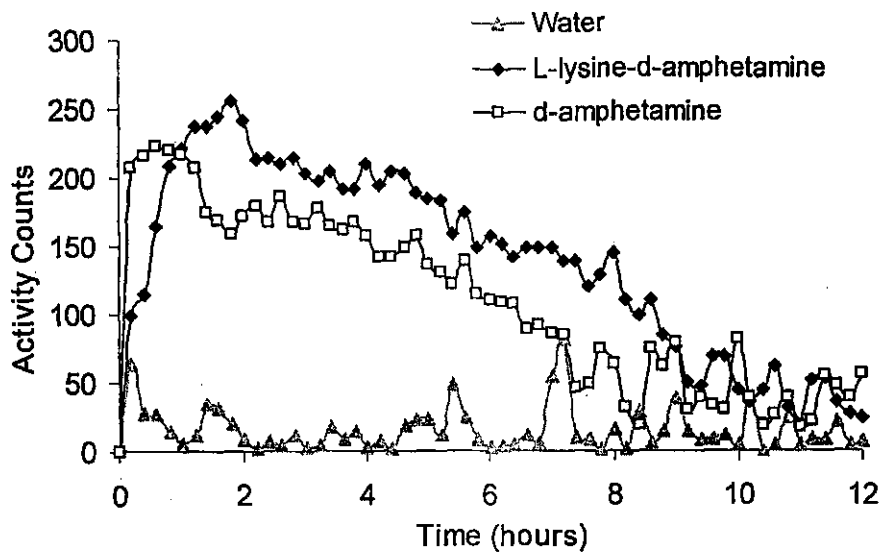

Water
L-lysine-d-amphetamine
d-amphetamine
Activity Counts
300
250
200
150
100
50
0
0
2
4
6
8
10
12
Time (hours)

Figure 38

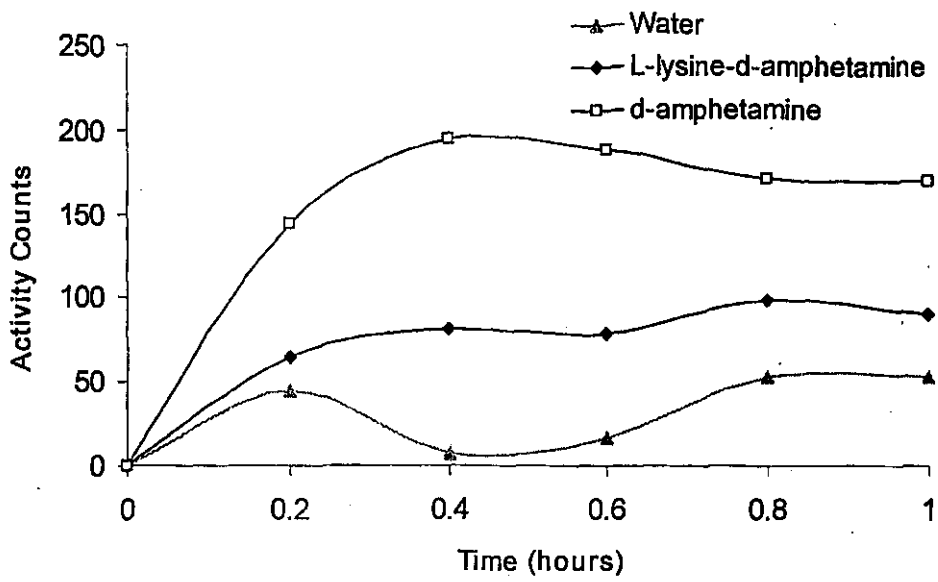

Water
L-lysine-d-amphetamine
d-amphetamine
250
200
150
100
50
0
Activity Counts
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 39

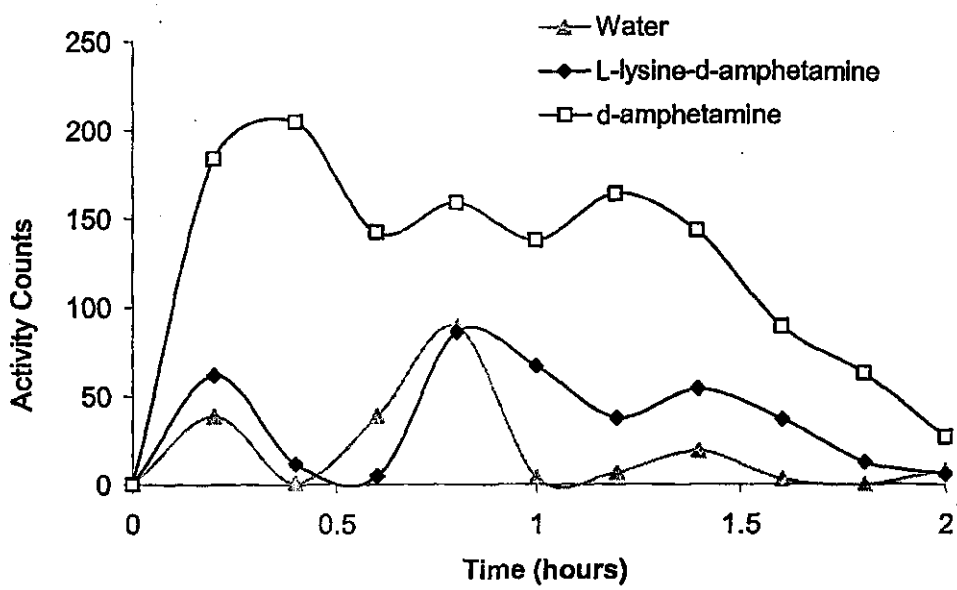

Water
L-lysine-d-amphetamine
d-amphetamine
250
200
150
100
50
0
Activity Counts
0
0.5
1
1.5
2
Time (hours)

Figure 40

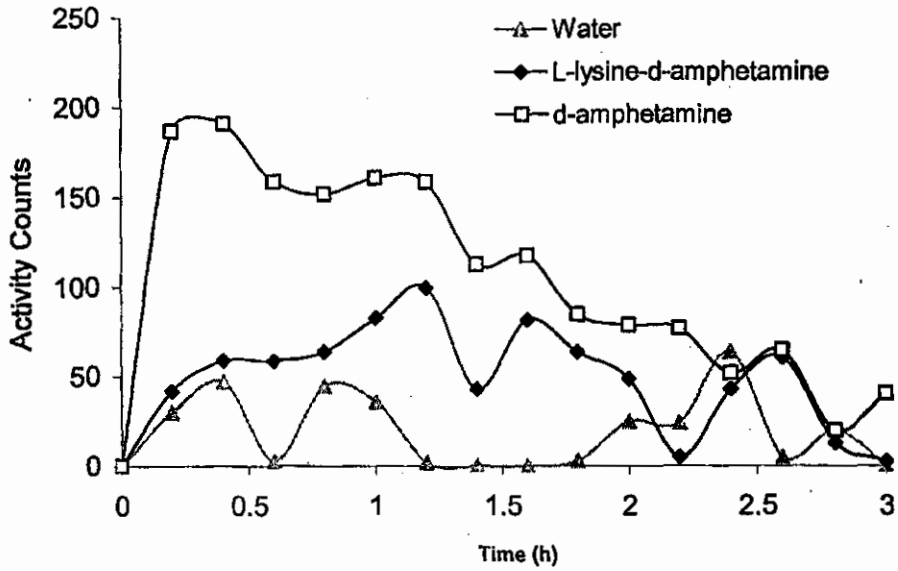

250
200
150
100
50
0
Activity Counts
0
0.5
1
1.5
2
2.5
3
Time (h)
Water
L-lysine-d-amphetamine
d-amphetamine

Figure 41

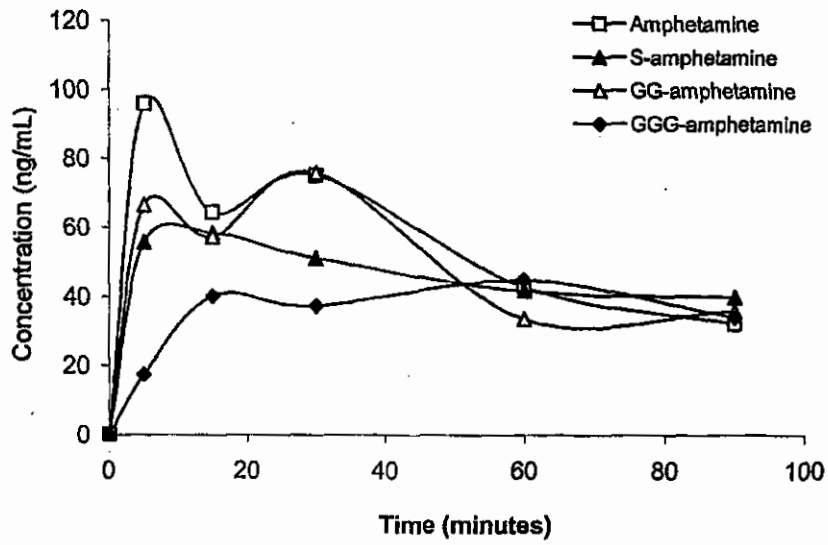

Amphetamine
S-amphetamine
GG-amphetamine
GGG-amphetamine
Concentration (ng/mL)
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (minutes)

Figure 42

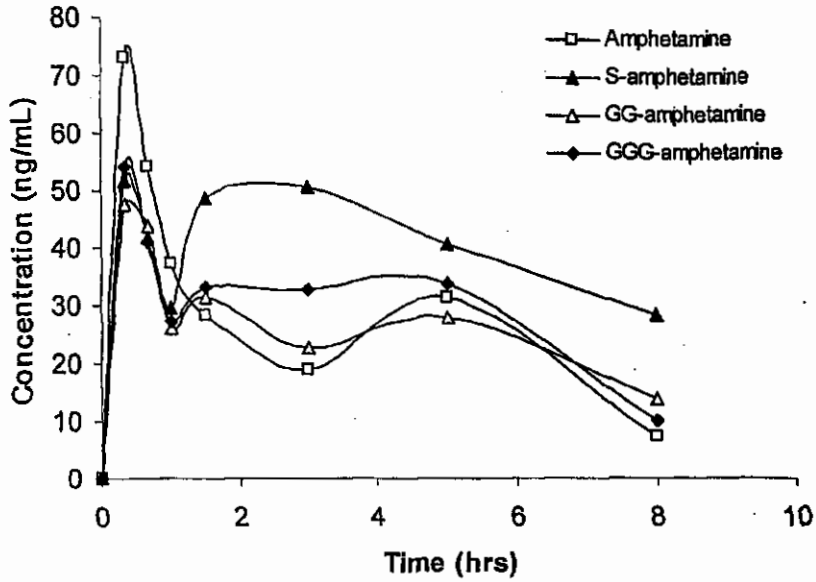

Concentration (ng/mL)
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
Time (hrs)
Amphetamine
S-amphetamine
GG-amphetamine
GGG-amphetamine

Figure 43

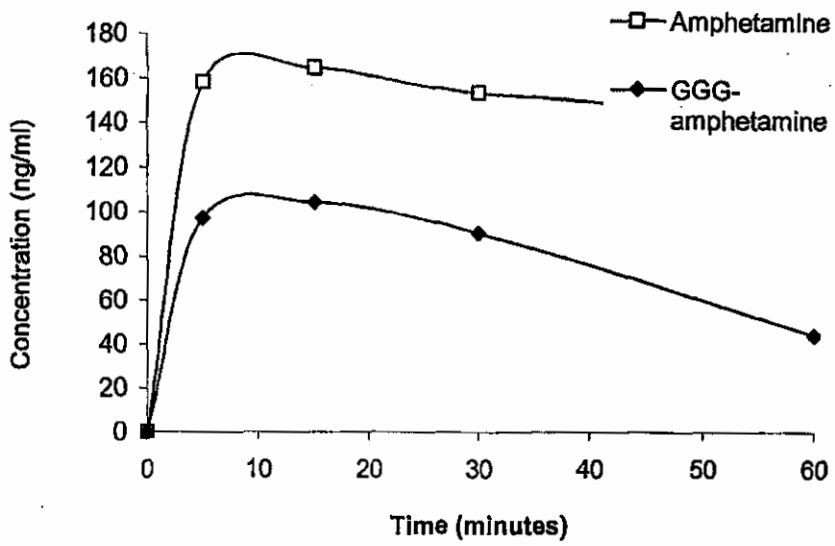

Amphetamine
GGG-amphetamine
Concentration (ng/ml)
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minutes)

Figure 44

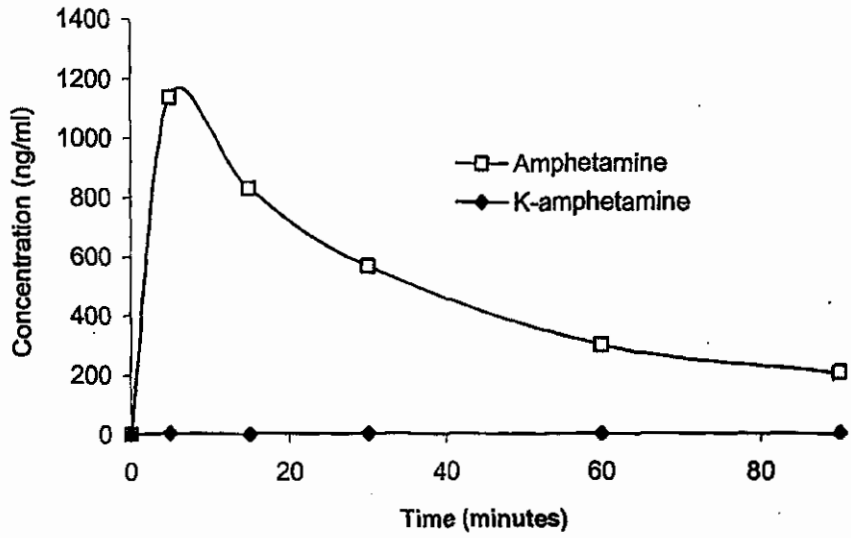

1400
1200
1000
800
600
400
200
0
Concentration (ng/ml)
0
20
40
60
80
Time (minutes)
Amphetamine
K-amphetamine

Figure 45

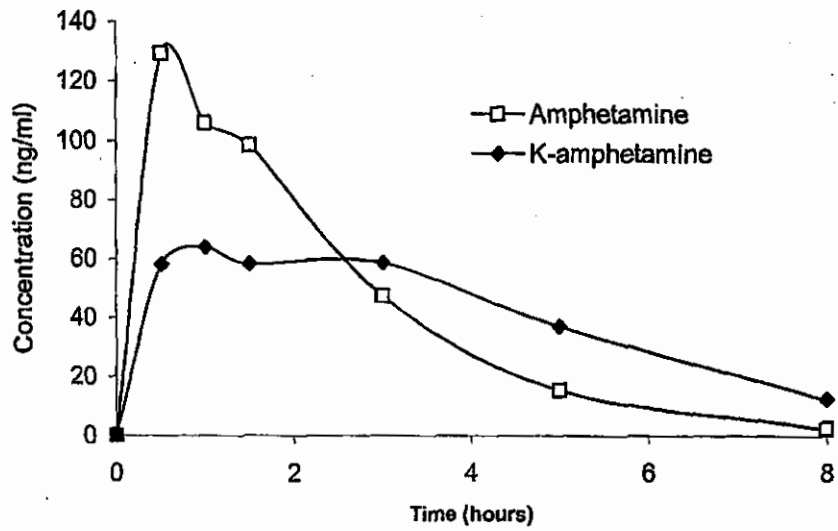

140
120
100
80
60
40
20
0
Concentration (ng/ml)
0
2
4
6
8
Time (hours)
Amphetamine
K-amphetamine

Figure 46

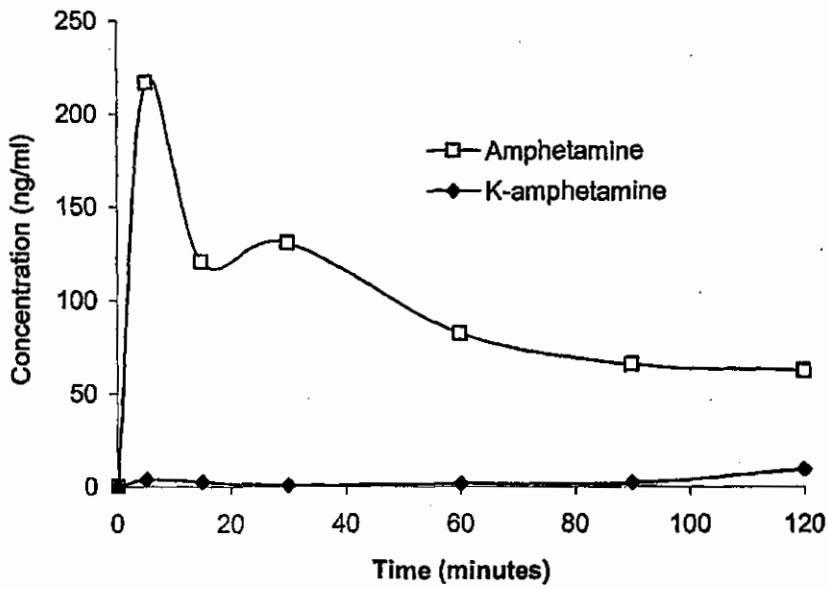

250
200
150
100
50
0
Concentration (ng/ml)
Amphetamine
K-amphetamine
0
20
40
60
80
100
120
Time (minutes)

Figure 47

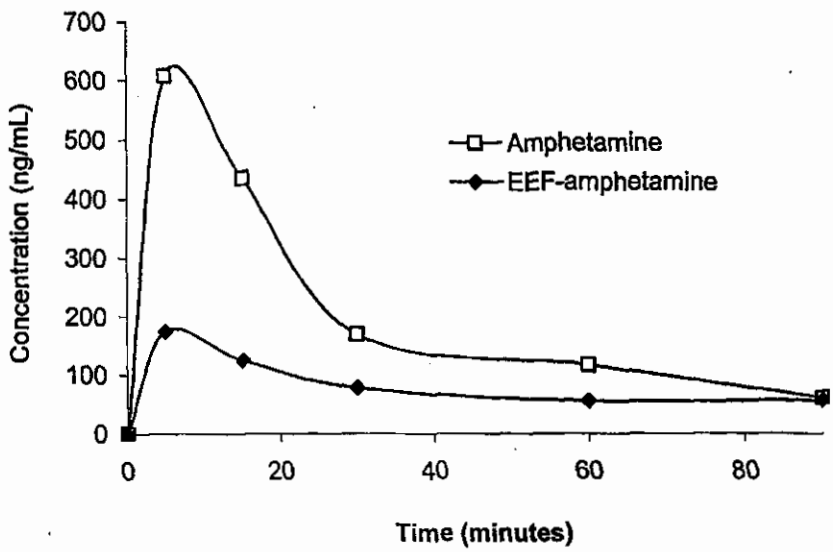

700
600
500
400
300
200
100
0
Concentration (ng/mL)
0
20
40
60
80
Time (minutes)
Amphetamine
EEF-amphetamine

Figure 48

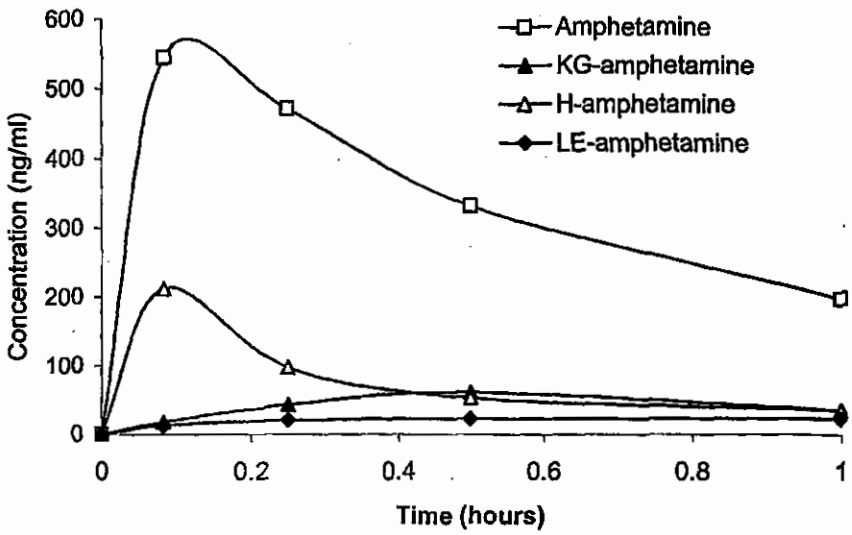

600
500
400
300
200
100
0
Concentration (ng/ml)
0
0.2
0.4
0.6
0.8
1
Time (hours)
Amphetamine
KG-amphetamine
H-amphetamine
LE-amphetamine

Figure 49

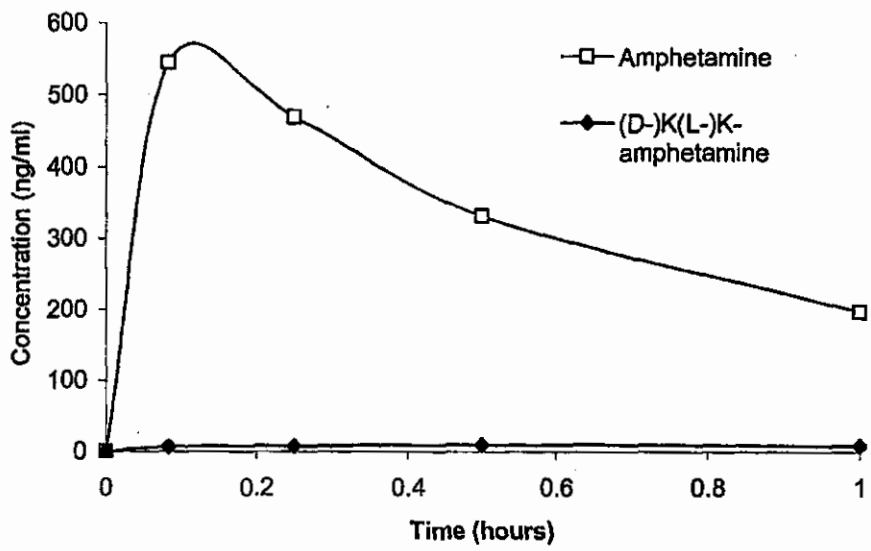

600
500
400
300
200
100
0
Concentration (ng/ml)
0
0.2
0.4
0.6
0.8
1
Time (hours)
Amphetamine
(D-)K(L-)K-amphetamine

Figure 50

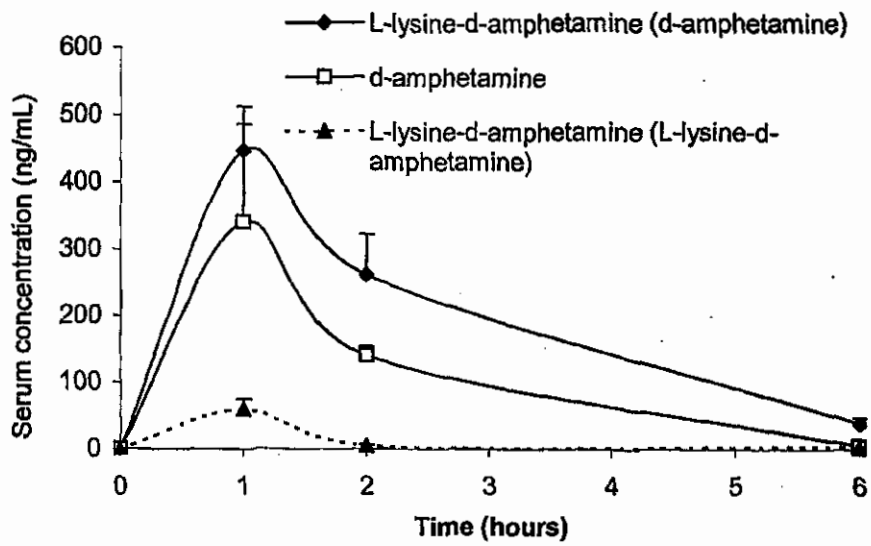


Figure 51A

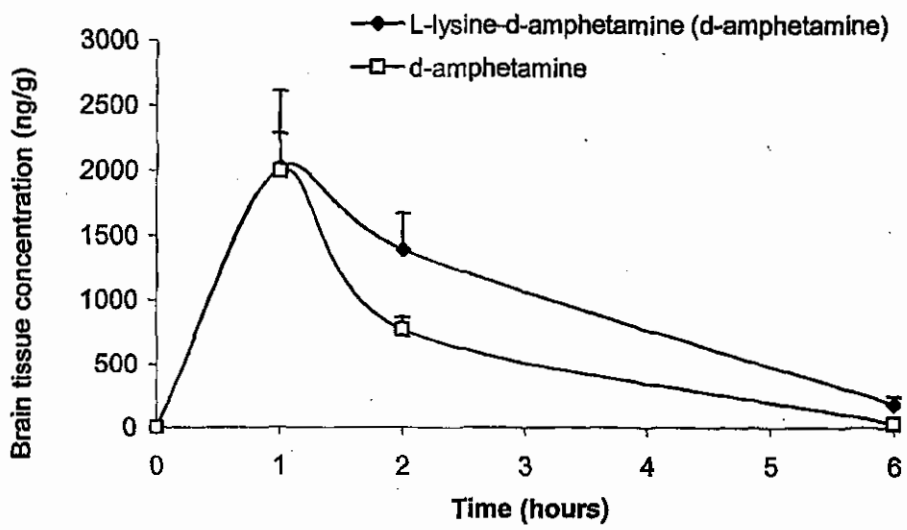
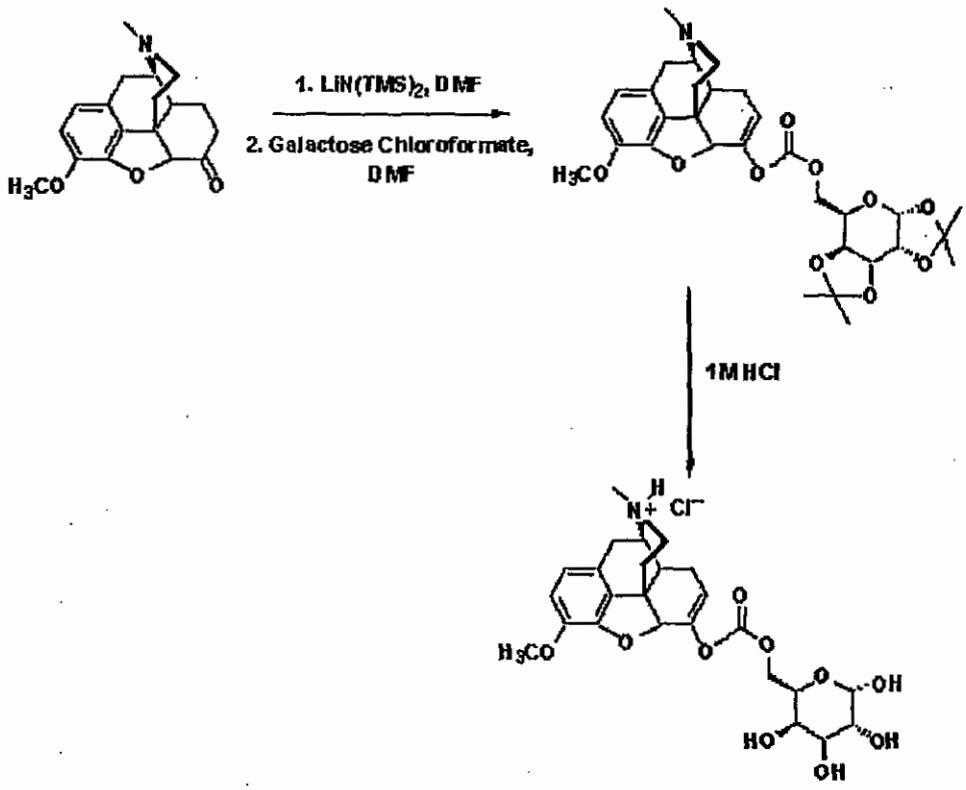


Figure 51B

Figure 52


1. LiN(TMS)2, DMF
2. Galactose Chloroformate, DMF
1M HCl
H3CO
Cl⁻
OH
HO

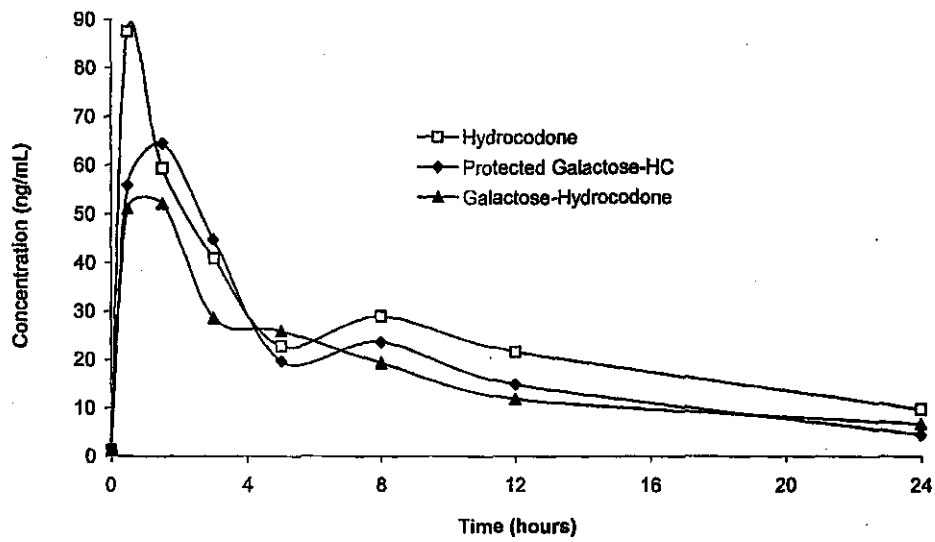
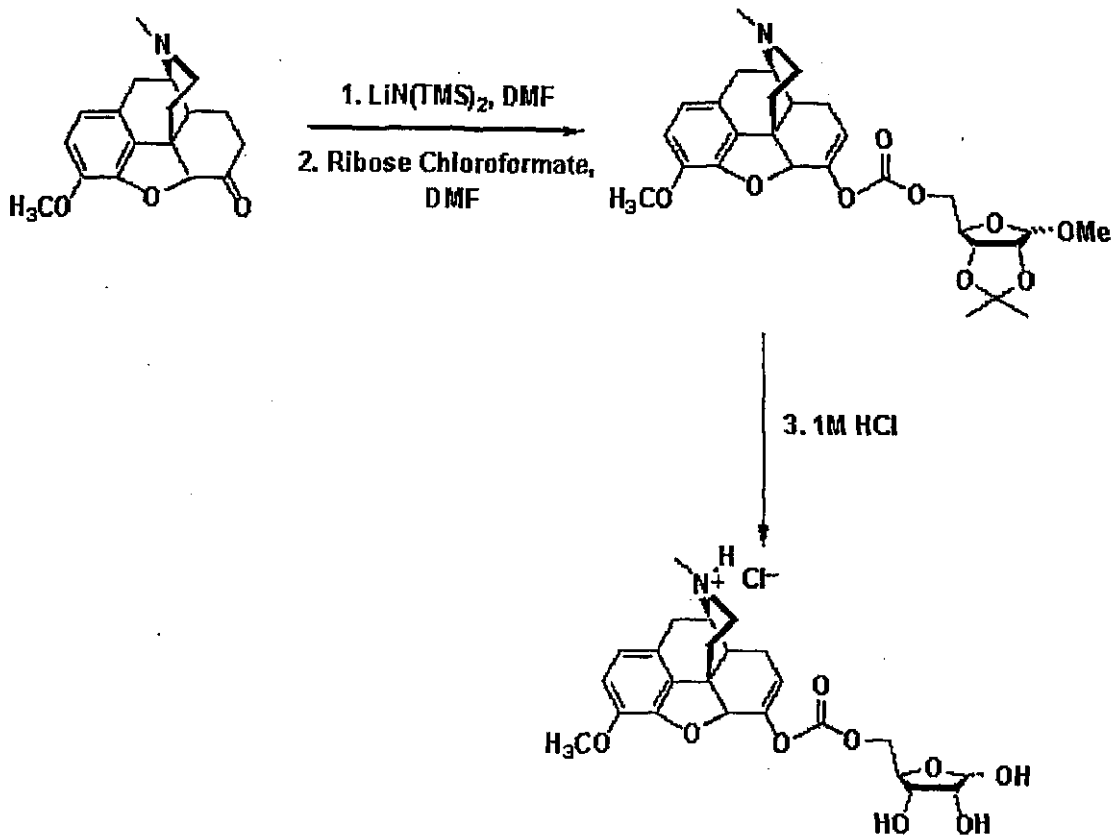

Concentration (ng/mL)
90
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
Time (hours)
Hydrocodone
Protected Galactose-HC
Galactose-Hydrocodone

Figure 53

Figure 54


1. LiN(TMS)2, DMF
2. Ribose Chloroformate, DMF
3. 1M HCl
N
H3CO
O
OMe
OH
HO
Cl-

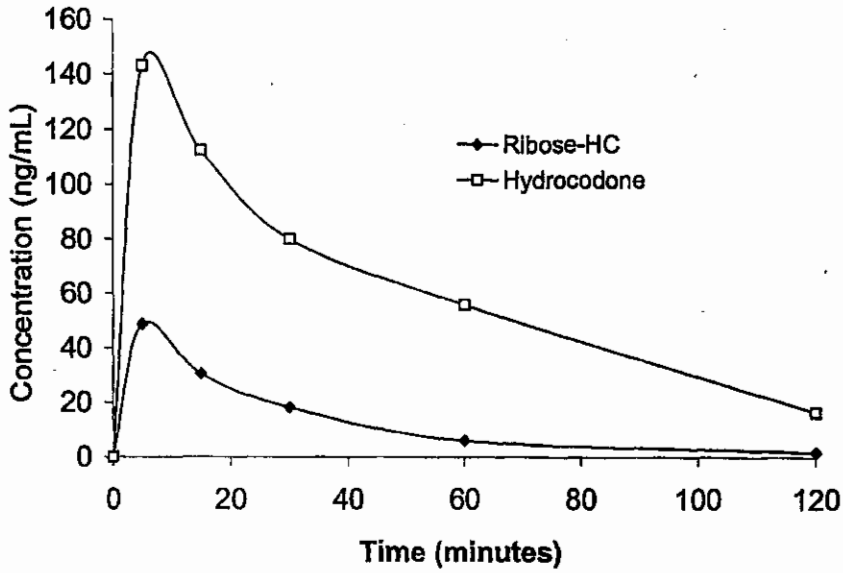

160
140
120
100
80
60
40
20
0
Concentration (ng/mL)
Ribose-HC
Hydrocodone
0
20
40
60
80
100
120
Time (minutes)

Figure 55

Figure 56


Hydrocodone
1. LiN(TMS)2, THF
2. Boc-Leu-OSu
Boc-Leu-Hydrocodone
4N HCl in dioxane
Leu-Hydrocodone

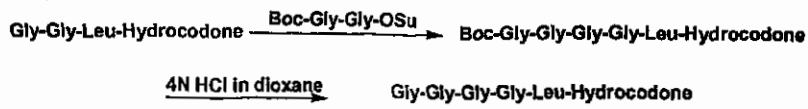
Figure 57


Pro-Hydrocodone
Boc-Ala-OSu
Boc-Ala-Pro-Hydrocodone
4N HCl in dioxane
Ala-Pro-Hydrocodone

Figure 58


Leu-Hydrocodone
Boc-Gly-Gly-OSu
Boc-Gly-Gly-Leu-Hydrocodone
4N HCl in dioxane
Gly-Gly-Leu-Hydrocodone

Figure 59


Gly-Gly-Leu-Hydrocodone
Boc-Gly-Gly-OSu
Boc-Gly-Gly-Gly-Gly-Leu-Hydrocodone
4N HCl in dioxane
Gly-Gly-Gly-Gly-Leu-Hydrocodone

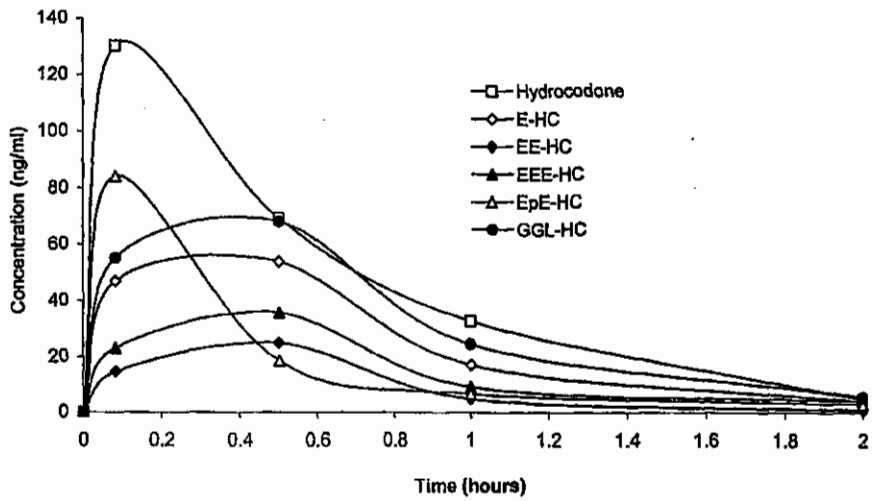

140
120
100
80
60
40
20
0
Concentration (ng/ml)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Time (hours)
Hydrocodone
E-HC
EE-HC
EEE-HC
EpE-HC
GGL-HC

Figure 60

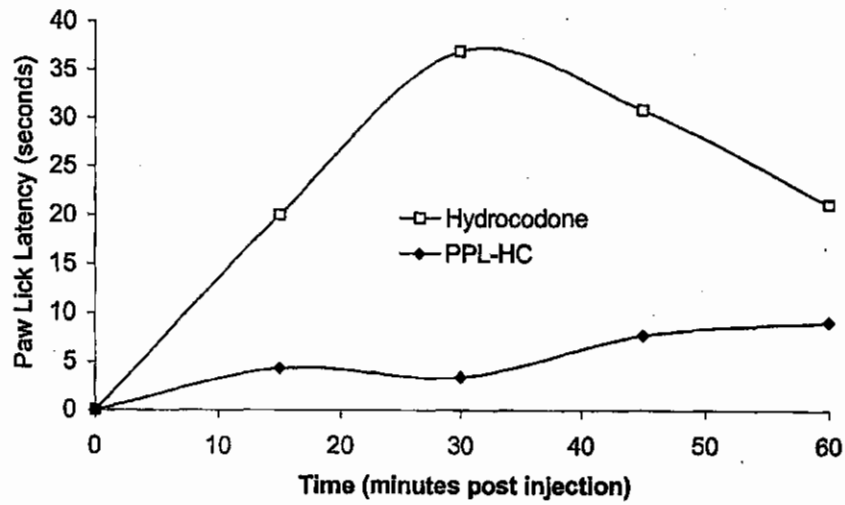

Paw Lick Latency (seconds)
40
35
30
25
20
15
10
5
0
0
10
20
30
40
50
60
Time (minutes post injection)
Hydrocodone
PPL-HC

Figure 61

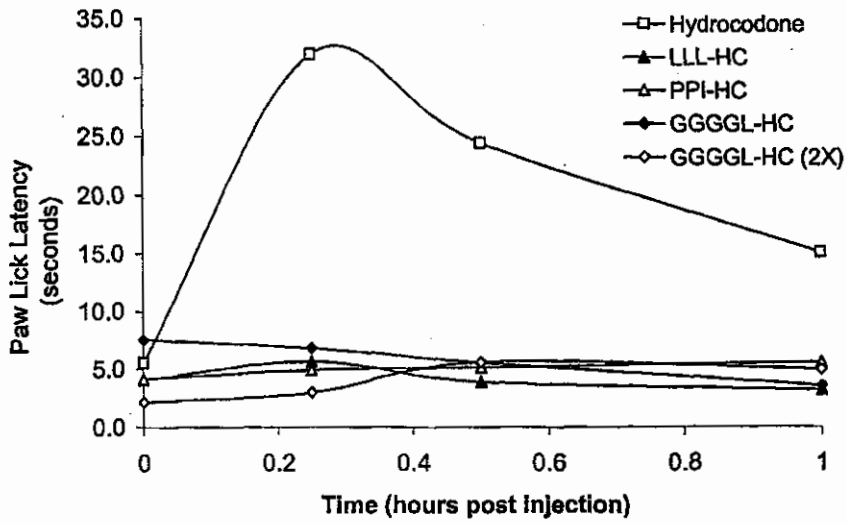

35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
Paw Lick Latency (seconds)
0
0.2
0.4
0.6
0.8
1
Time (hours post injection)
Hydrocodone
LLL-HC
PPI-HC
GGGGL-HC
GGGGL-HC (2X)

Figure 62

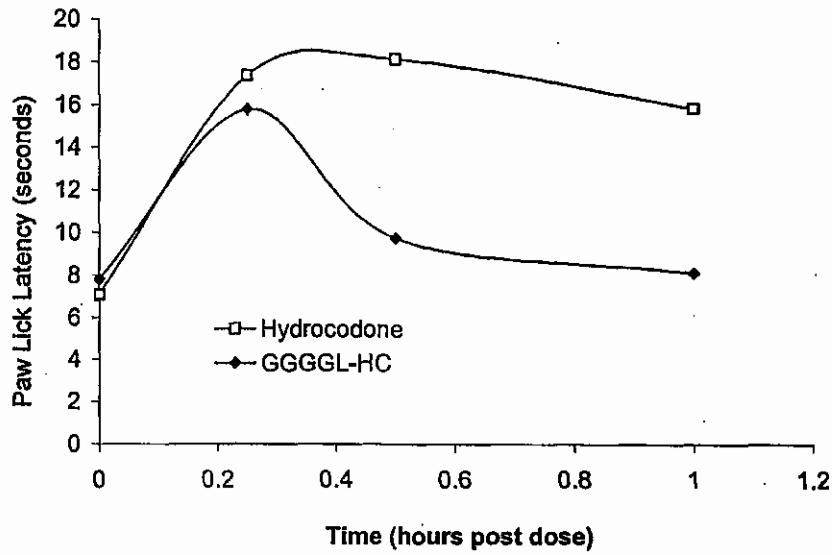

Paw Lick Latency (seconds)
20
18
16
14
12
10
8
6
4
2
0
0
0.2
0.4
0.6
0.8
1
1.2
Hydrocodone
GGGGL-HC
Time (hours post dose)

Figure 63

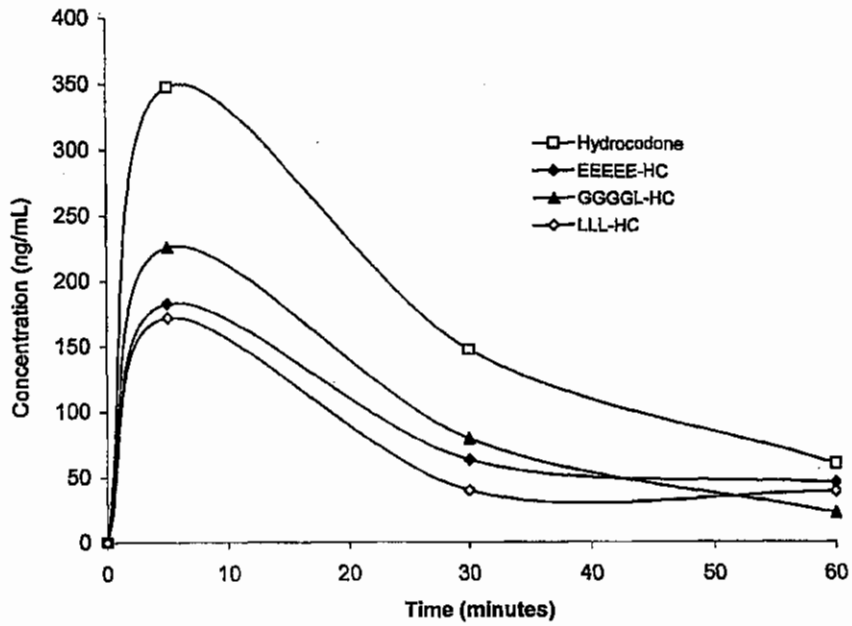

400
350
300
250
200
150
100
50
0
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
EEEEE-HC
GGGGL-HC
LLL-HC

Figure 64

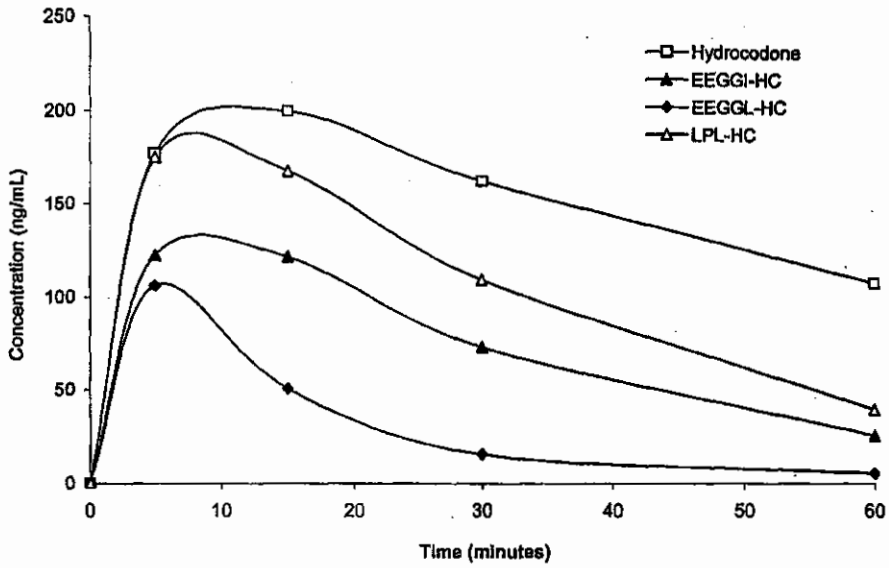

250
200
150
100
50
0
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
EEGGI-HC
EEGGL-HC
LPL-HC

Figure 65

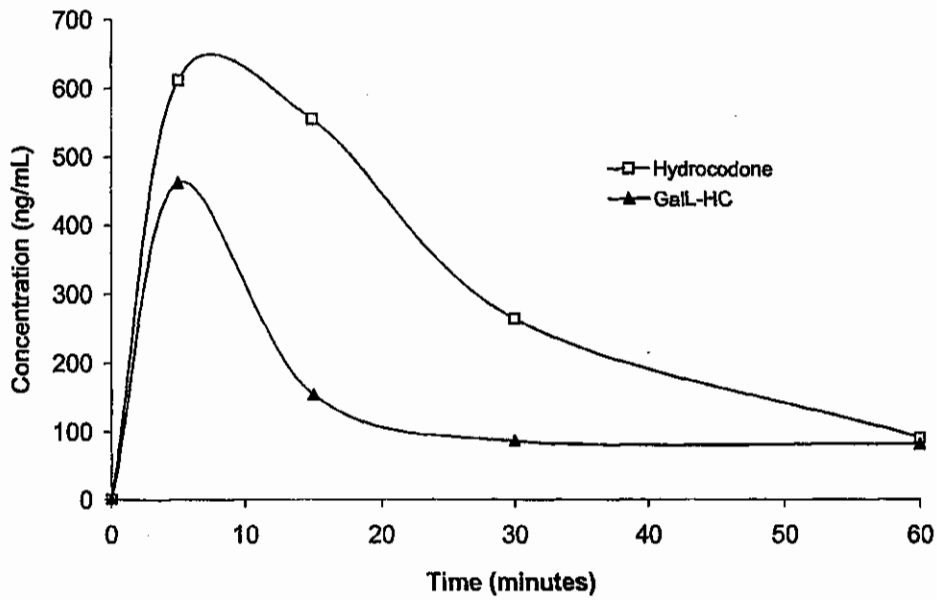

700
600
500
400
300
200
100
0
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
GalL-HC

Figure 66

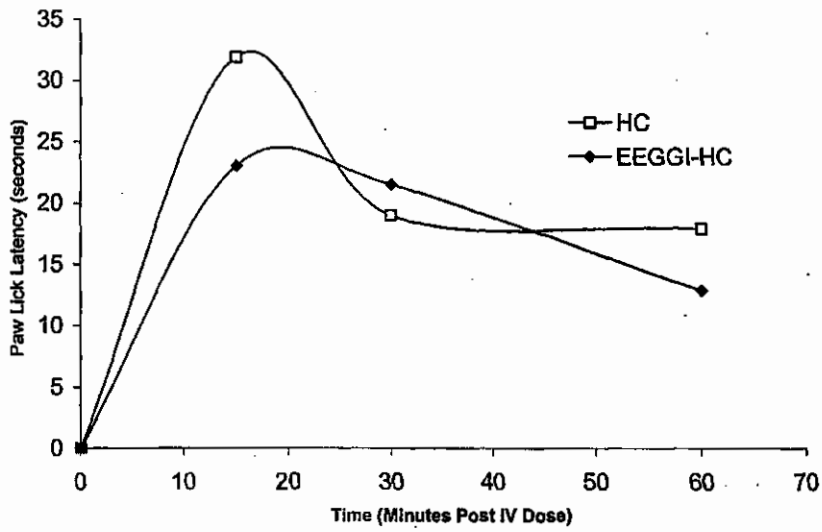

35
30
25
20
15
10
5
0
Paw Lick Latency (seconds)
0
10
20
30
40
50
60
70
Time (Minutes Post IV Dose)
HC
EEGGI-HC

Figure 67

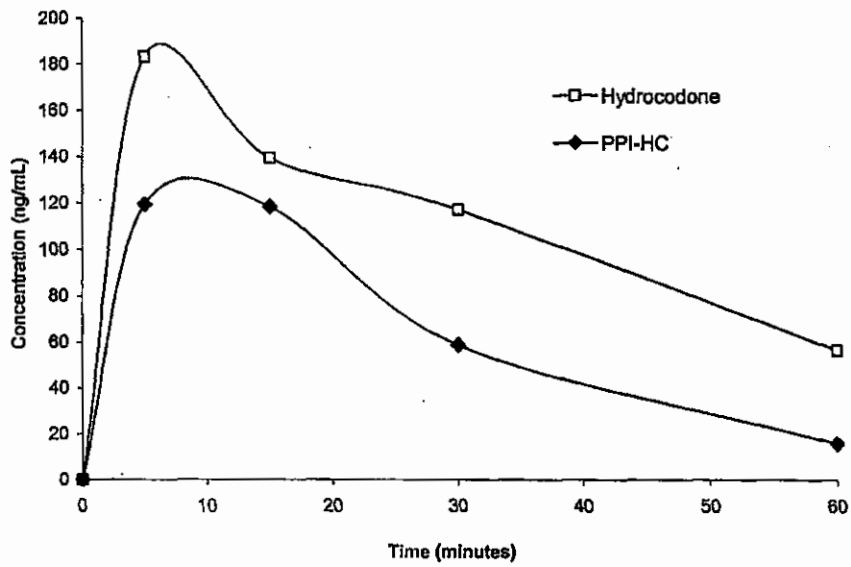

200
180
160
140
120
100
80
60
40
20
0
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
PPI-HC

Figure 68

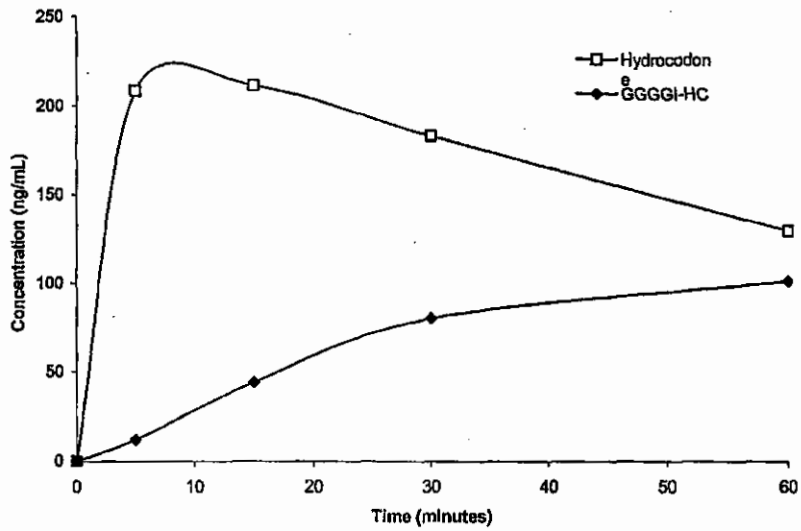

250
200
150
100
50
0
Concentration (ng/mL)
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
GGGGI-HC

Figure 69

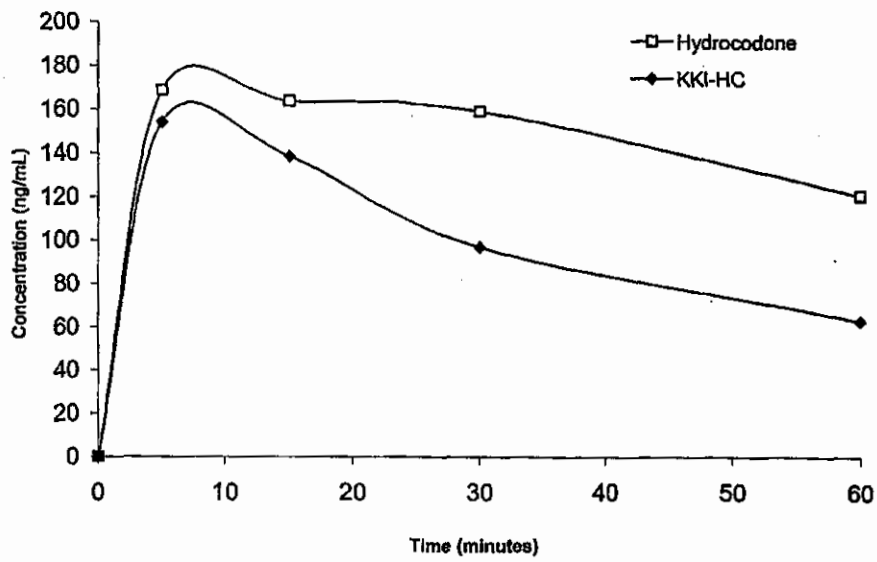

Hydrocodone
KKI-HC
Concentration (ng/mL)
200
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minutes)

Figure 70

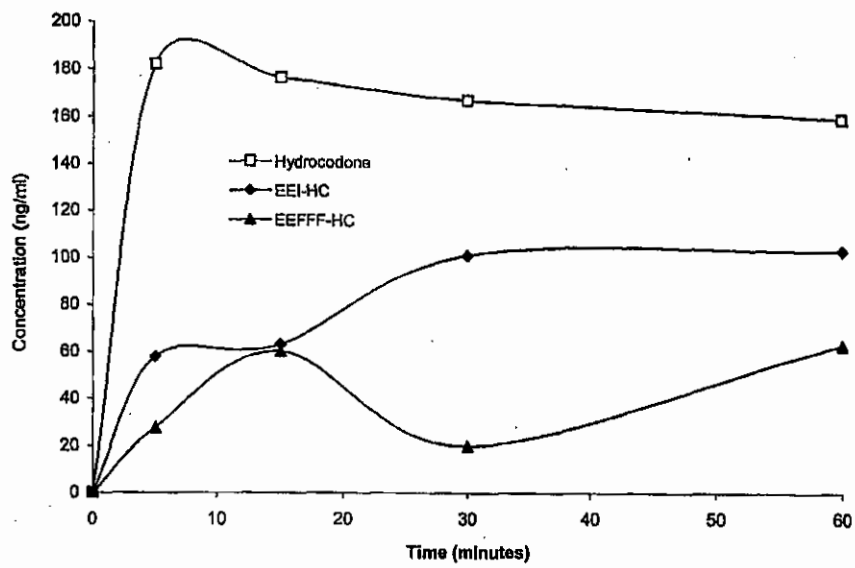

Concentration (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
EEI-HC
EEFFF-HC

Figure 71

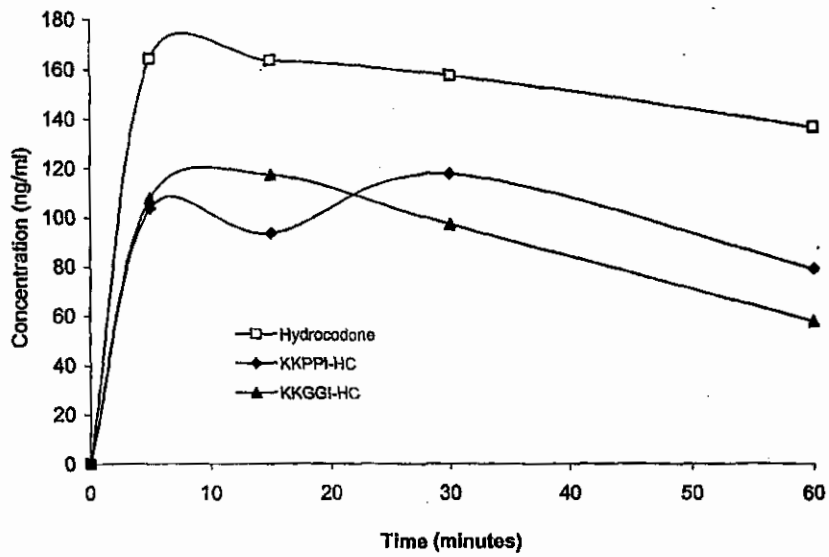

180
160
140
120
100
80
60
40
20
0
Concentration (ng/ml)
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
KKPPI-HC
KKGGI-HC

Figure 72

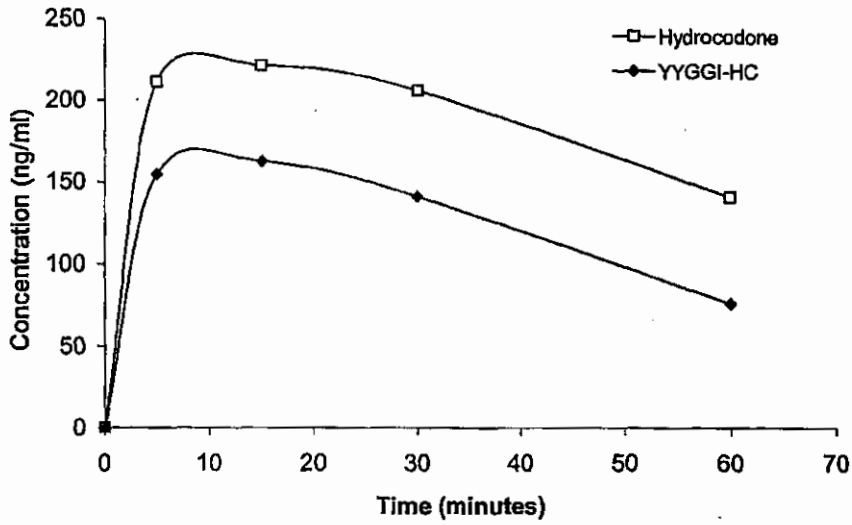

250
200
150
100
50
0
Concentration (ng/ml)
0
10
20
30
40
50
60
70
Time (minutes)
Hydrocodone
YYGGI-HC

Figure 73

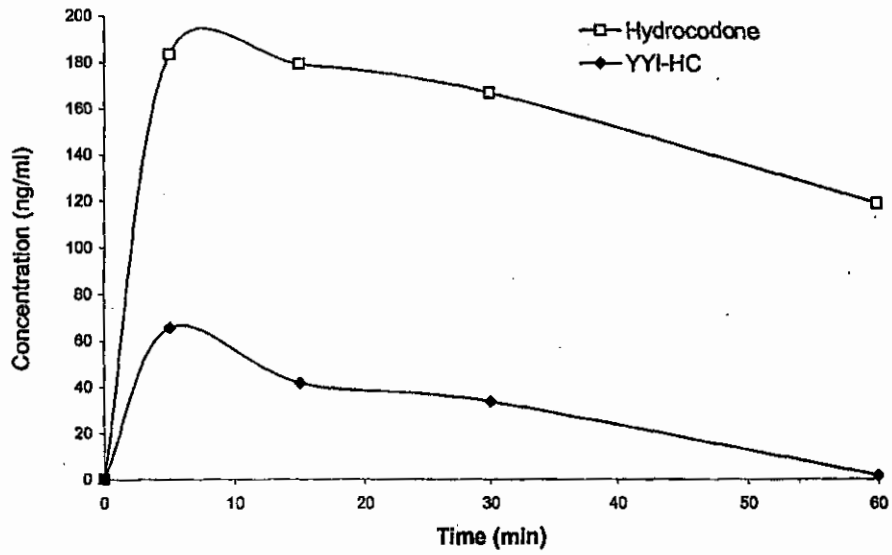

Hydrocodone
YYI-HC
Concentration (ng/ml)
Time (min)
0
20
40
60
80
100
120
140
160
180
200
0
10
20
30
40
50
60

Figure 74

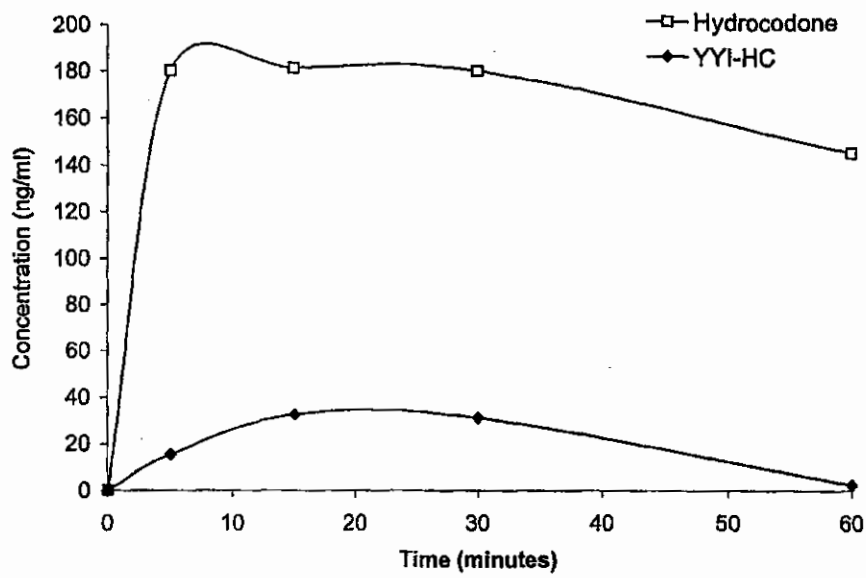

Hydrocodone
YYI-HC
Concentration (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minutes)

Figure 75

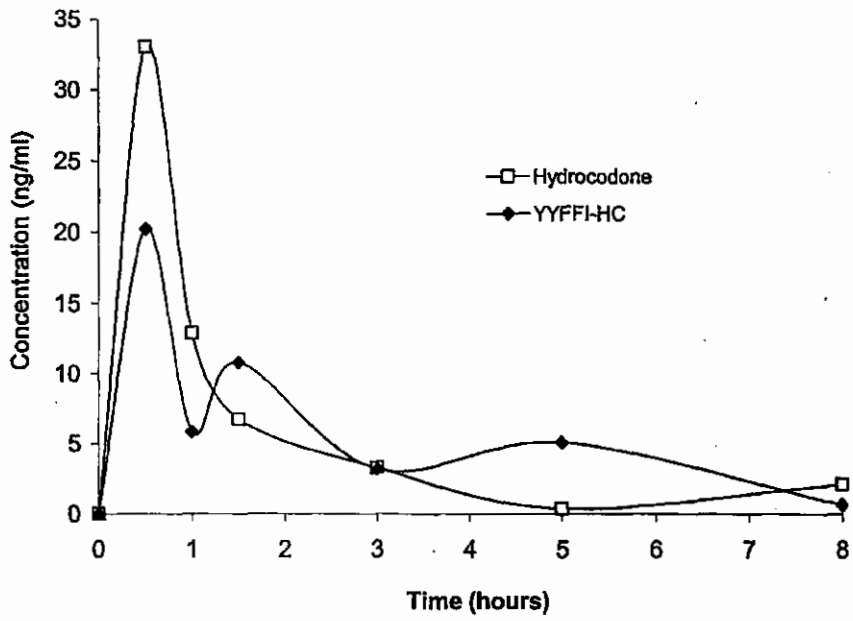

35
30
25
20
15
10
5
0
Concentration (ng/ml)
0
1
2
3
4
5
6
7
8
Time (hours)
Hydrocodone
YYFFI-HC

Figure 76

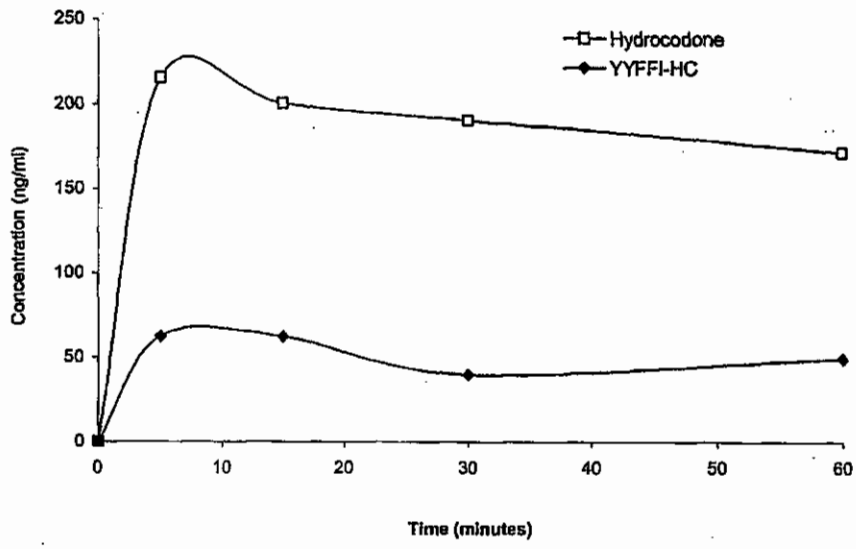

250
200
150
100
50
0
Concentration (ng/ml)
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
YYFFI-HC

Figure 77

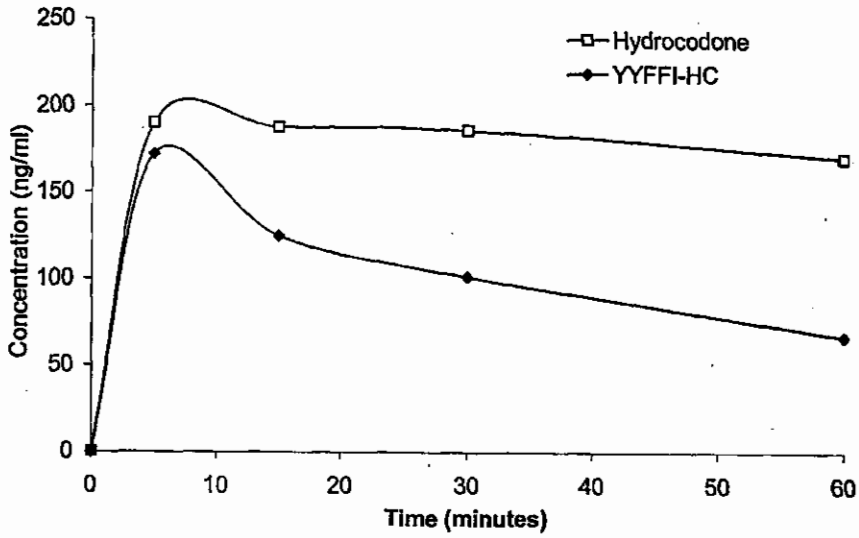

250
200
150
100
50
0
Concentration (ng/ml)
0
10
20
30
40
50
60
Time (minutes)
Hydrocodone
YYFFI-HC

Figure 78

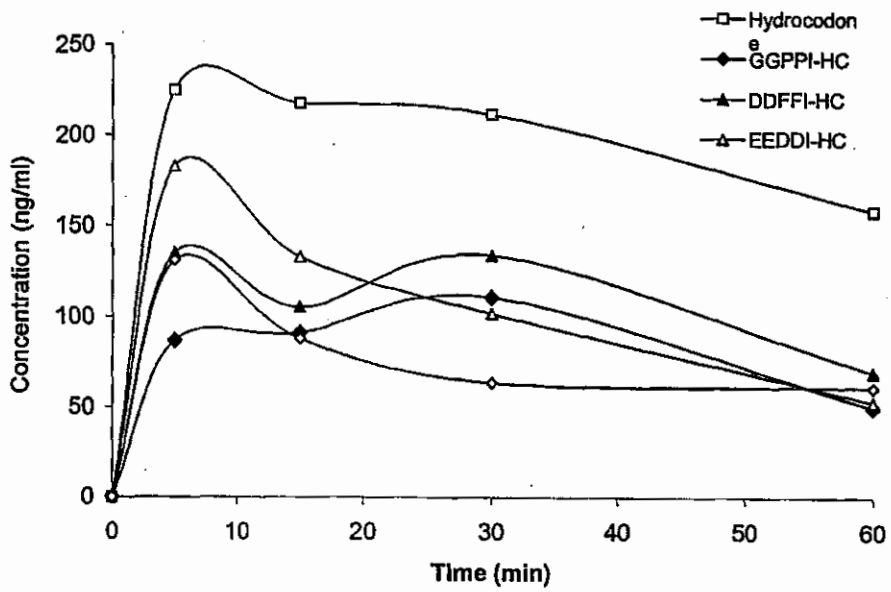

Hydrocodone
GGPPI-HC
DDFFI-HC
EEDDI-HC
Concentration (ng/ml)
250
200
150
100
50
0
0
10
20
30
40
50
60
Time (min)

Figure 79

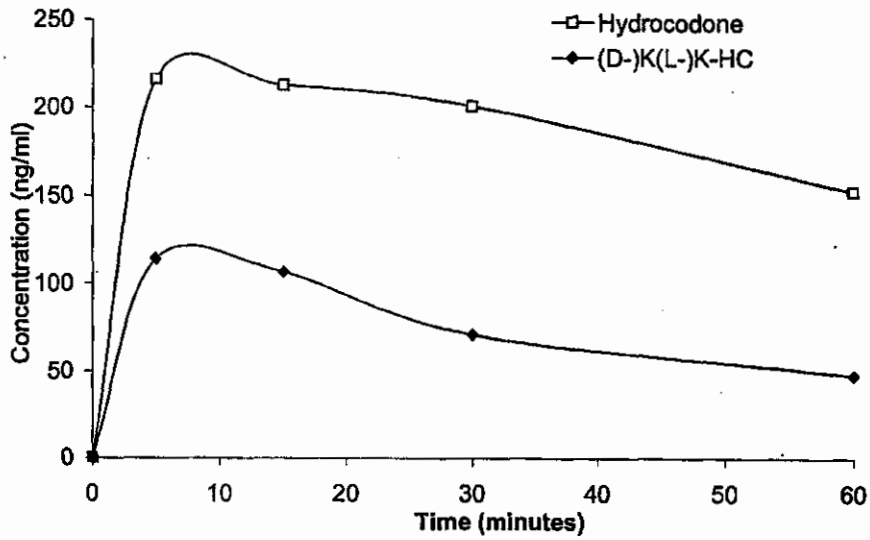

Hydrocodone
(D-)K(L-)K-HC
Concentration (ng/ml)
250
200
150
100
50
0
0
10
20
30
40
50
60
Time (minutes)

Figure 80

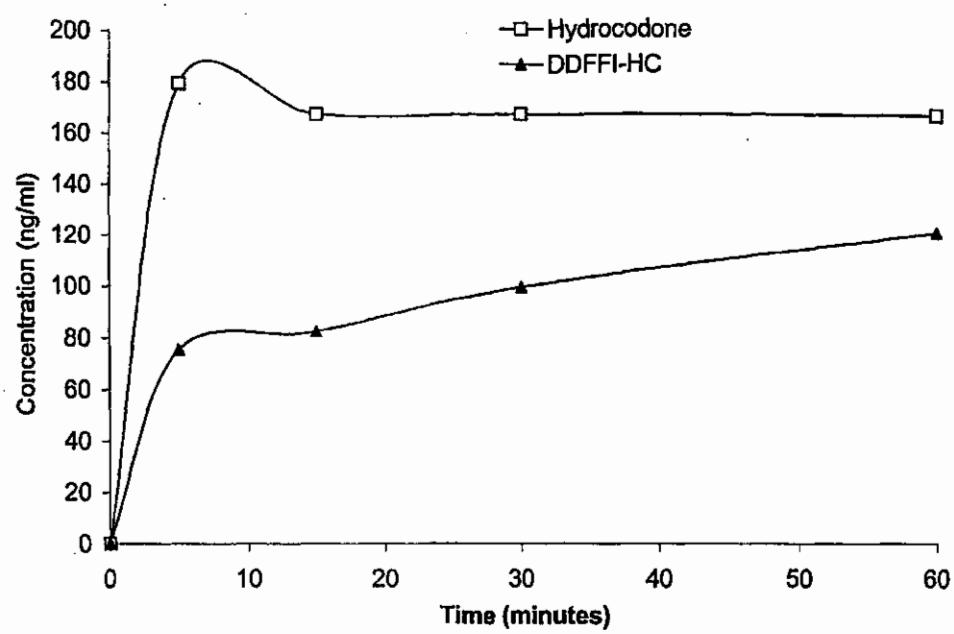

Hydrocodone
DDFFI-HC
Concentration (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
10
20
30
40
50
60
Time (minutes)

Figure 81

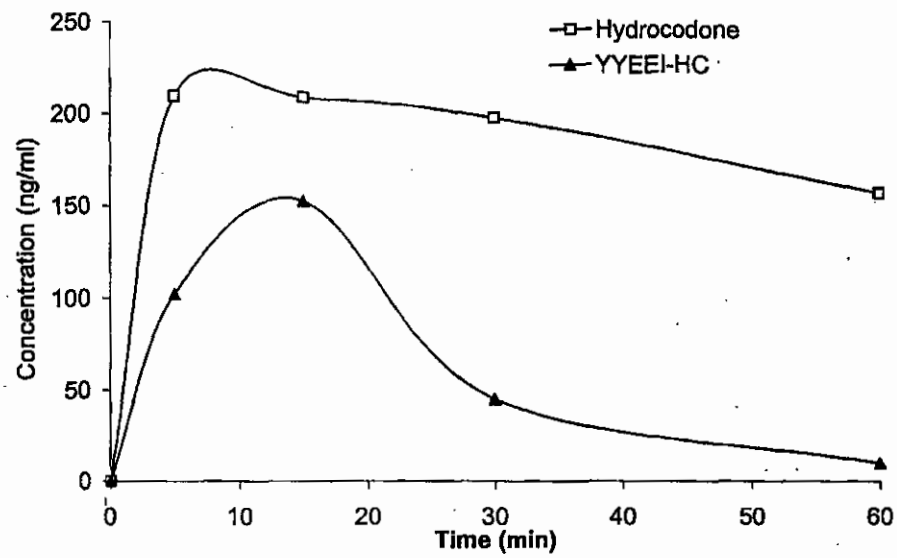

Hydrocodone
YYEEI-HC
Concentration (ng/ml)
250
200
150
100
50
0
0
10
20
30
40
50
60
Time (min)

Figure 82

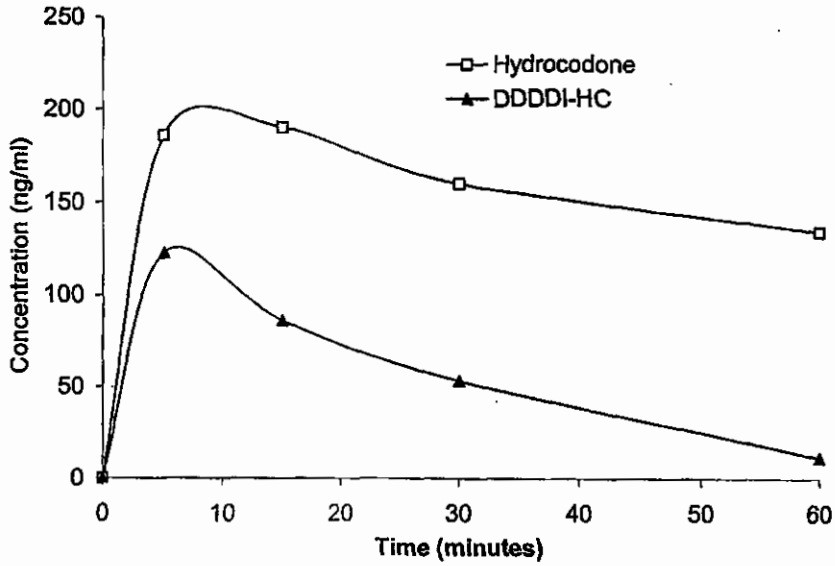

250
200
150
100
50
0
Concentration (ng/ml)
Hydrocodone
DDDDI-HC
0
10
20
30
40
50
60
Time (minutes)

Figure 83

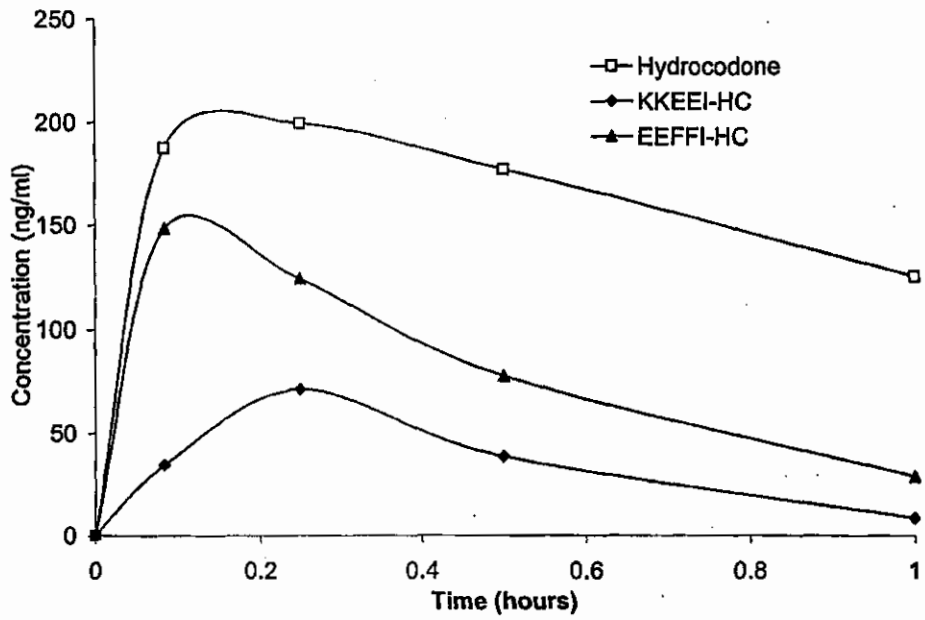

250
200
150
100
50
0
Concentration (ng/ml)
0
0.2
0.4
0.6
0.8
1
Time (hours)
Hydrocodone
KKEEI-HC
EEFFI-HC

Figure 84

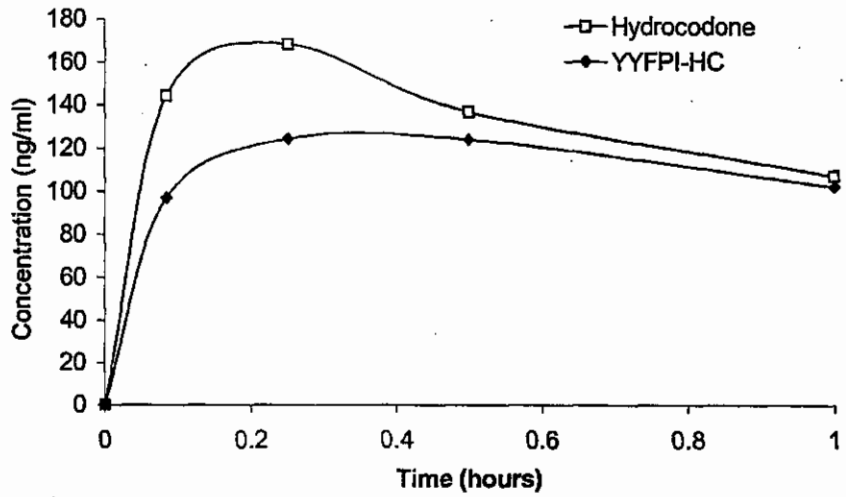
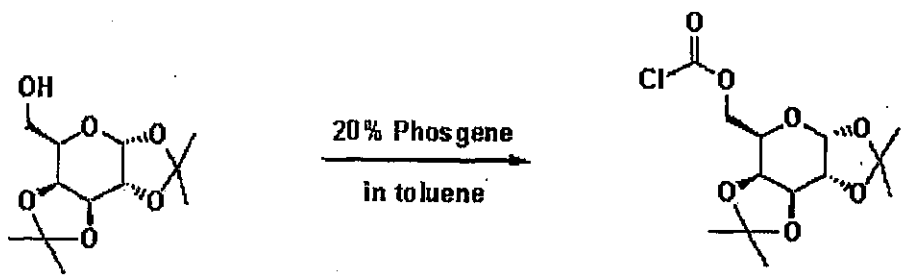

Hydrocodone
YYFPI-HC
Concentration (ng/ml)
180
160
140
120
100
80
60
40
20
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 85

Figure 86



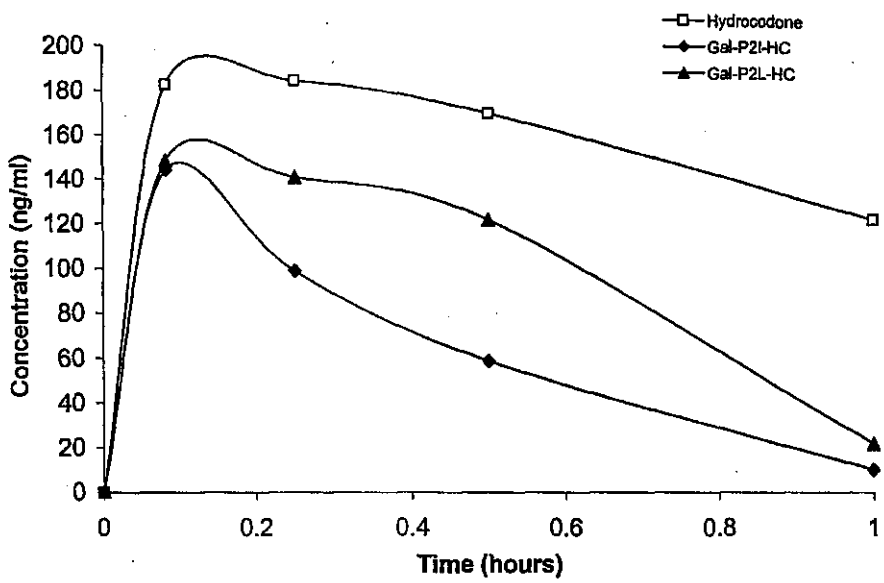

Hydrocodone
Gal-P2I-HC
Gal-P2L-HC
Concentration (ng/ml)
200
180
160
140
120
100
80
60
40
20
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 87

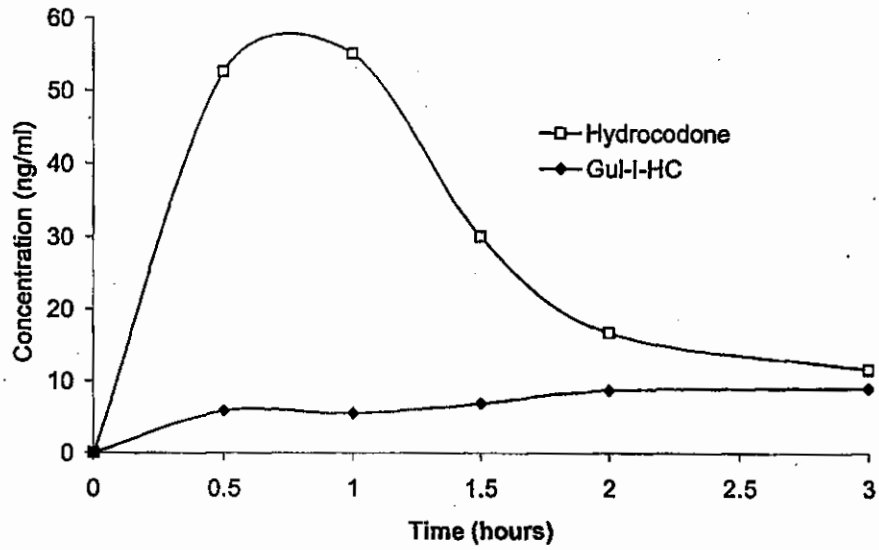
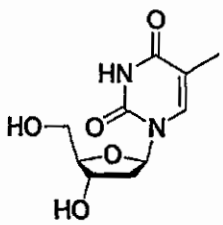
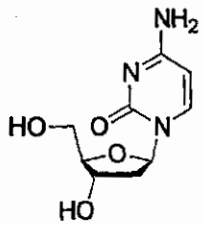

60
50
40
30
20
10
0
Concentration (ng/ml)
0
0.5
1
1.5
2
2.5
3
Time (hours)
Hydrocodone
Gul-I-HC

Figure 88

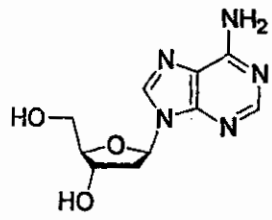
Figure 89



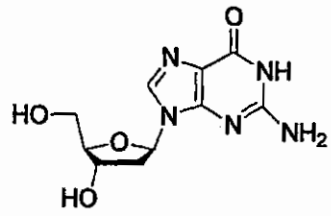
Thymidine



2'-deoxycytidine

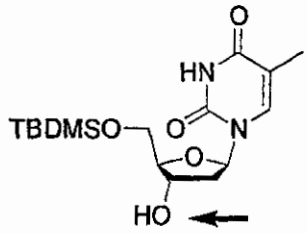


2'-deoxyadenosine



2'-deoxyguanosine

Representative Nucleosides



al Conjugation Site

Protected Thymidine

Site of Conjugation for Hydrocodone

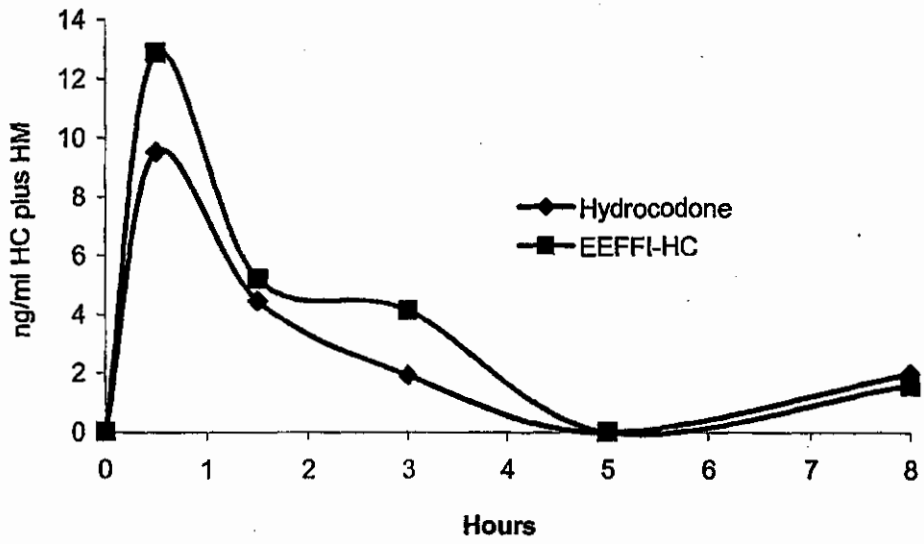

14
12
10
8
6
4
2
0
ng/ml HC plus HM
0
1
2
3
4
5
6
7
8
Hours
Hydrocodone
EEFFI-HC

Figure 90

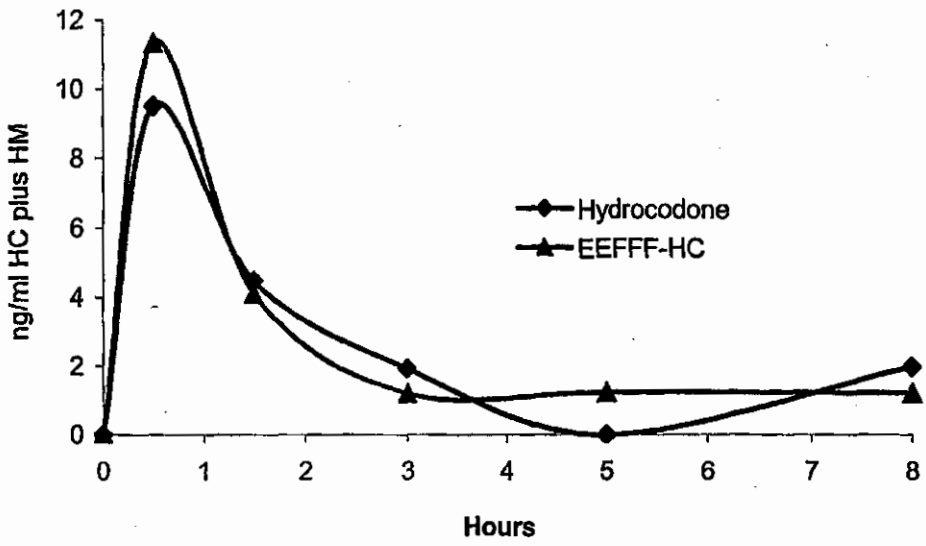

12
10
8
6
4
2
0
ng/ml HC plus HM
0
1
2
3
4
5
6
7
8
Hours
Hydrocodone
EEFFF-HC

Figure 91

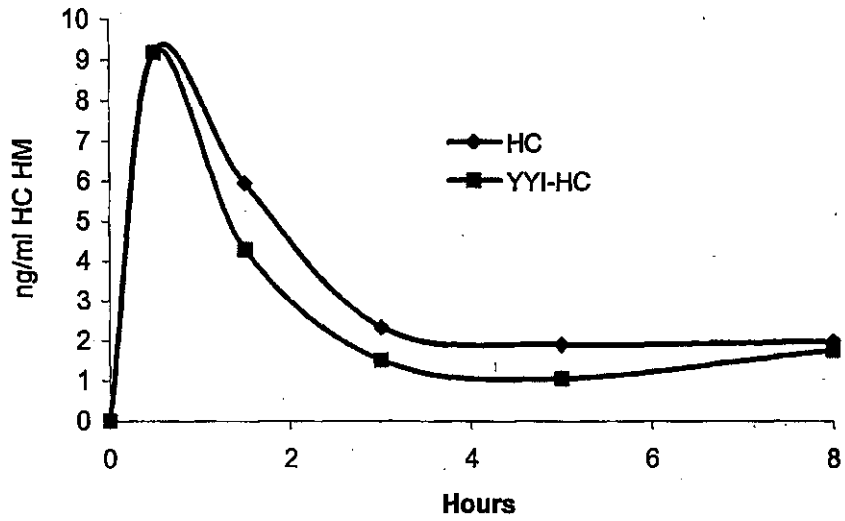


Figure 92

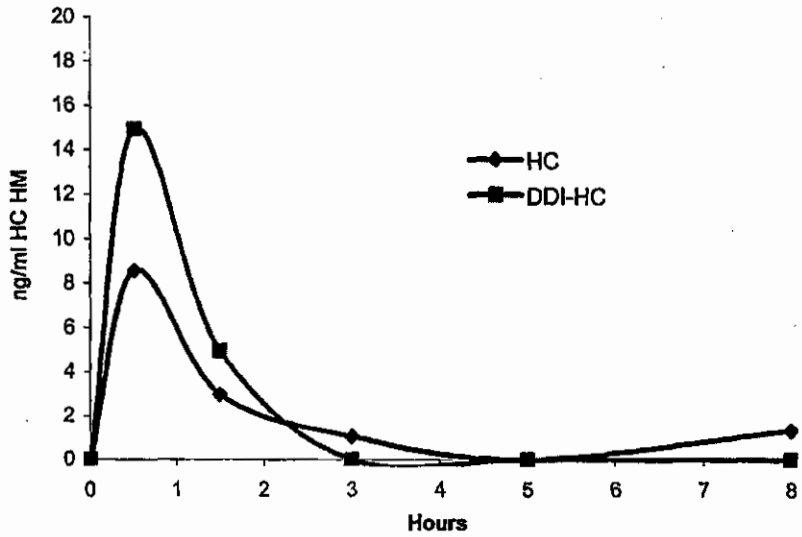


Figure 93

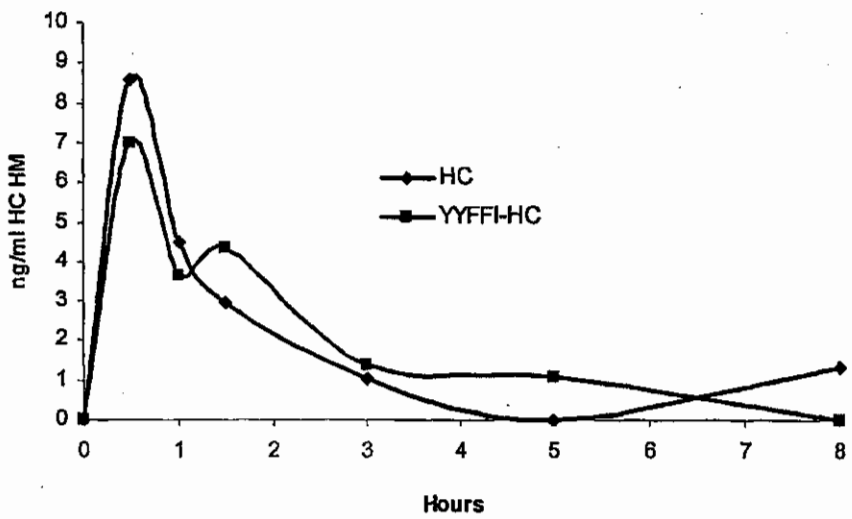


Figure 94

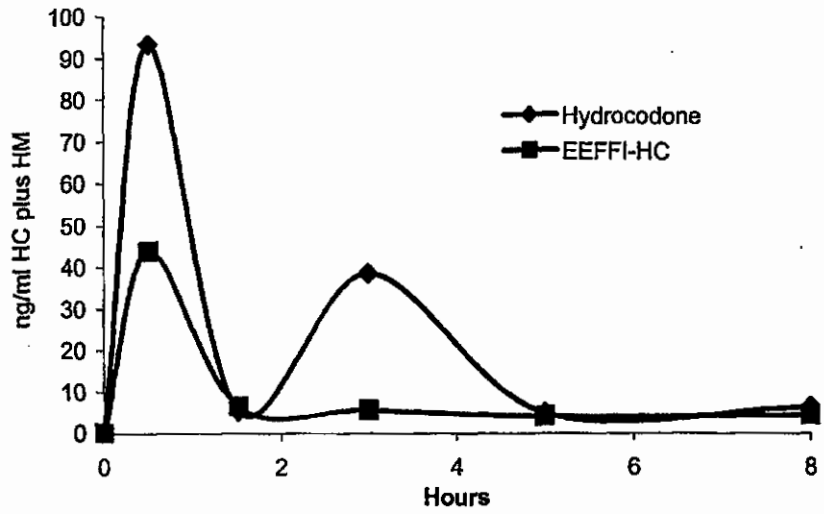

100
90
80
70
60
50
40
30
20
10
0
ng/ml HC plus HM
0
2
4
6
8
Hours
Hydrocodone
EEFFI-HC

Figure 95

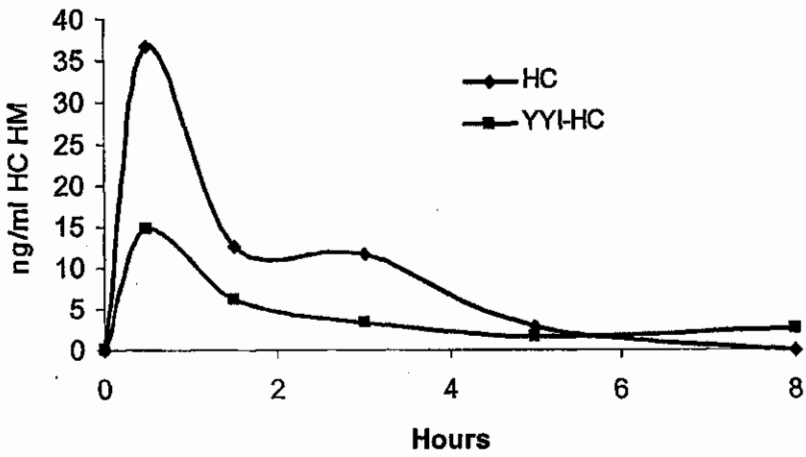


Figure 96

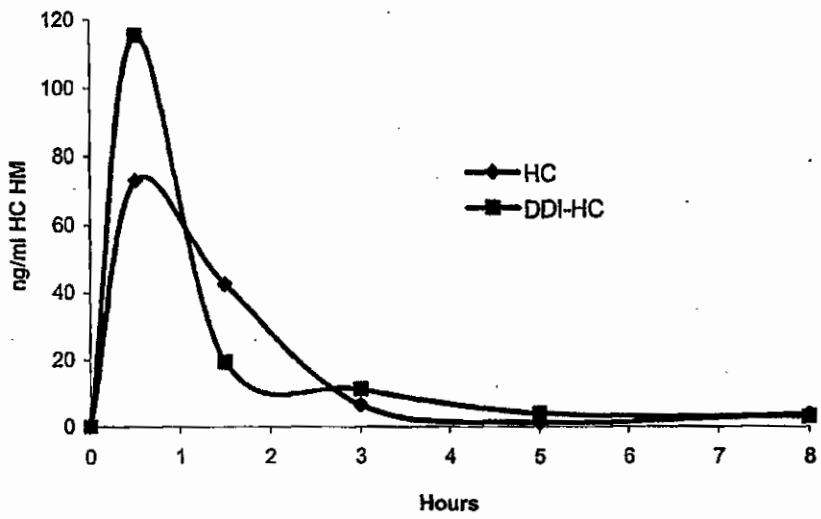


Figure 97

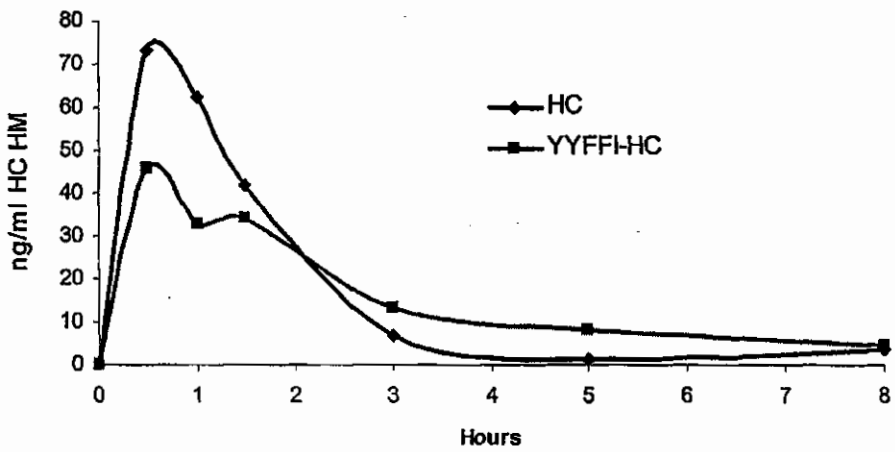


Figure 98

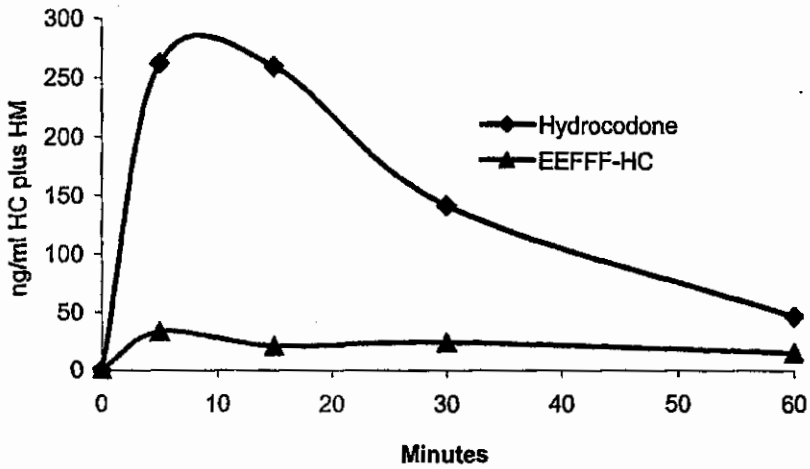

300
250
200
150
100
50
0
ng/ml HC plus HM
0
10
20
30
40
50
60
Minutes
Hydrocodone
EEFFF-HC

Figure 99

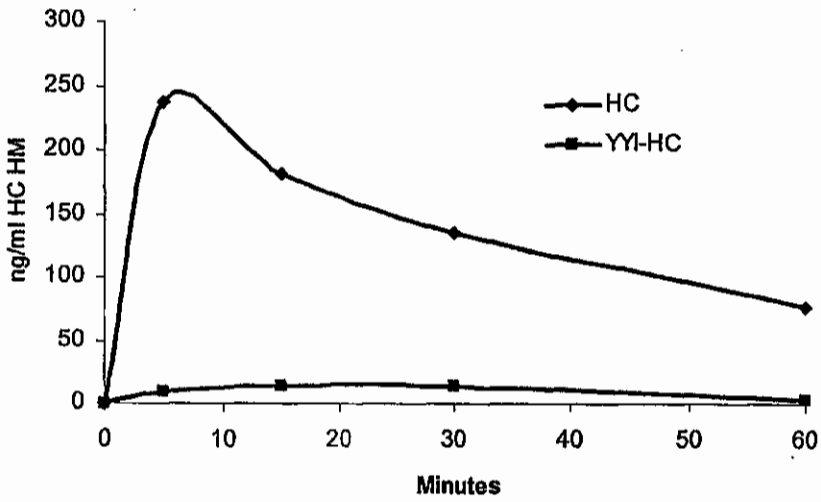

300
250
200
150
100
50
0
ng/ml HC HM
0
10
20
30
40
50
60
Minutes
HC
YYI-HC

Figure 100

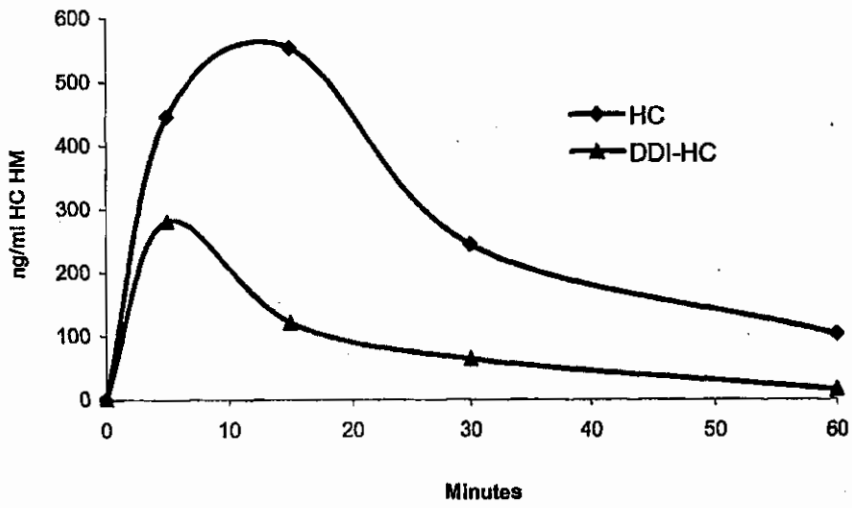

600
500
400
300
200
100
0
ng/ml HC HM
0
10
20
30
40
50
60
Minutes
HC
DDI-HC

Figure 101

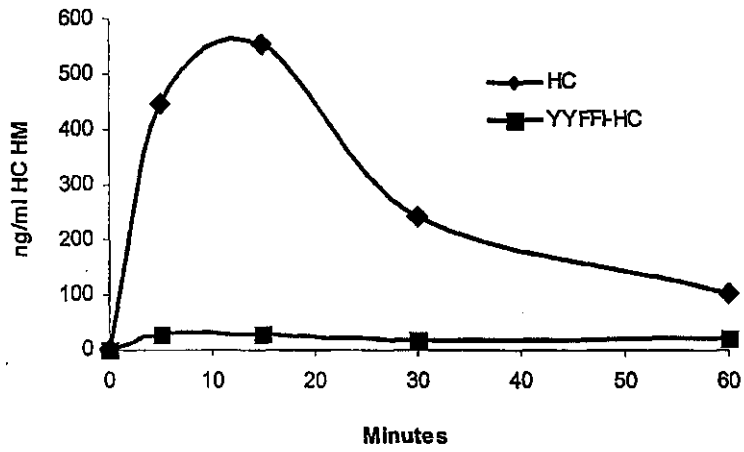

600
500
400
300
200
100
0
ng/ml HC HM
0
10
20
30
40
50
60
Minutes
HC
YYFFI-HC

Figure 102

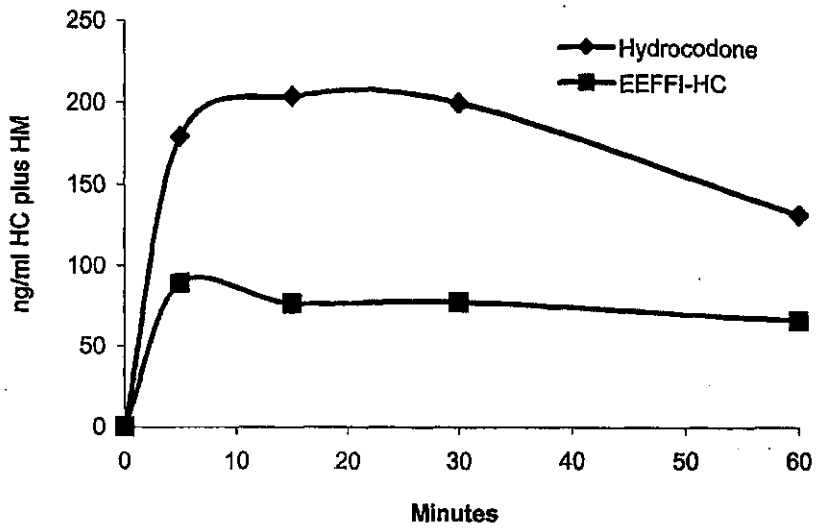

250
200
150
100
50
0
ng/ml HC plus HM
0
10
20
30
40
50
60
Minutes
Hydrocodone
EEFFI-HC

Figure 103

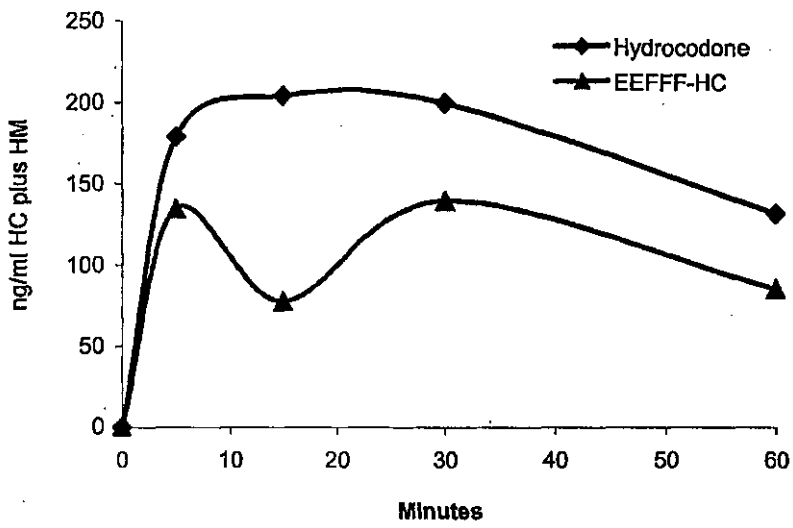

250
200
150
100
50
0
ng/ml HC plus HM
0
10
20
30
40
50
60
Minutes
Hydrocodone
EEFFF-HC

Figure 104

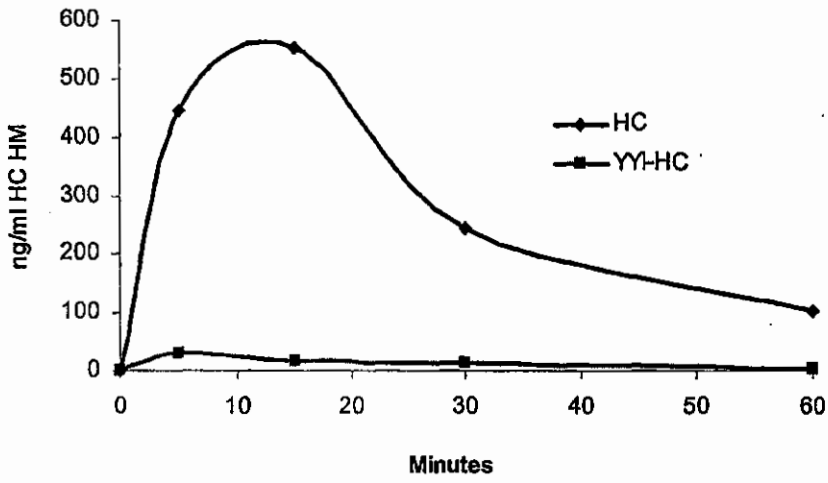

600
500
400
300
200
100
0
ng/ml HC HM
0
10
20
30
40
50
60
Minutes
HC
YYI-HC

Figure 105

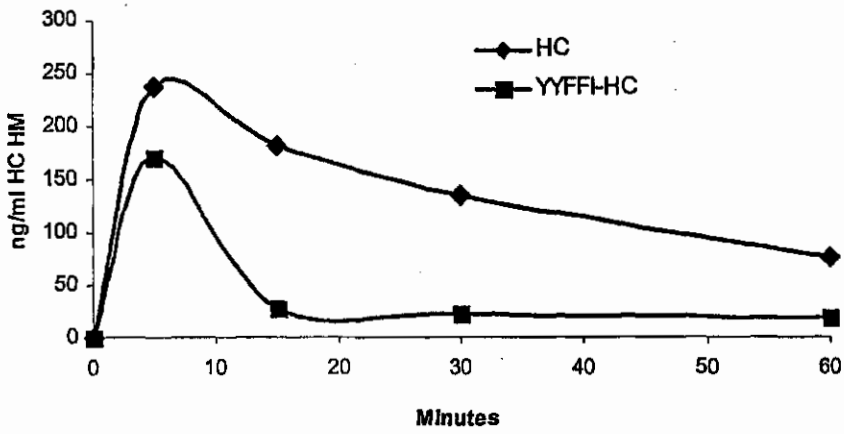

300
250
200
150
100
50
0
ng/ml HC HM
0
10
20
30
40
50
60
Minutes
HC
YYFFI-HC

Figure 106

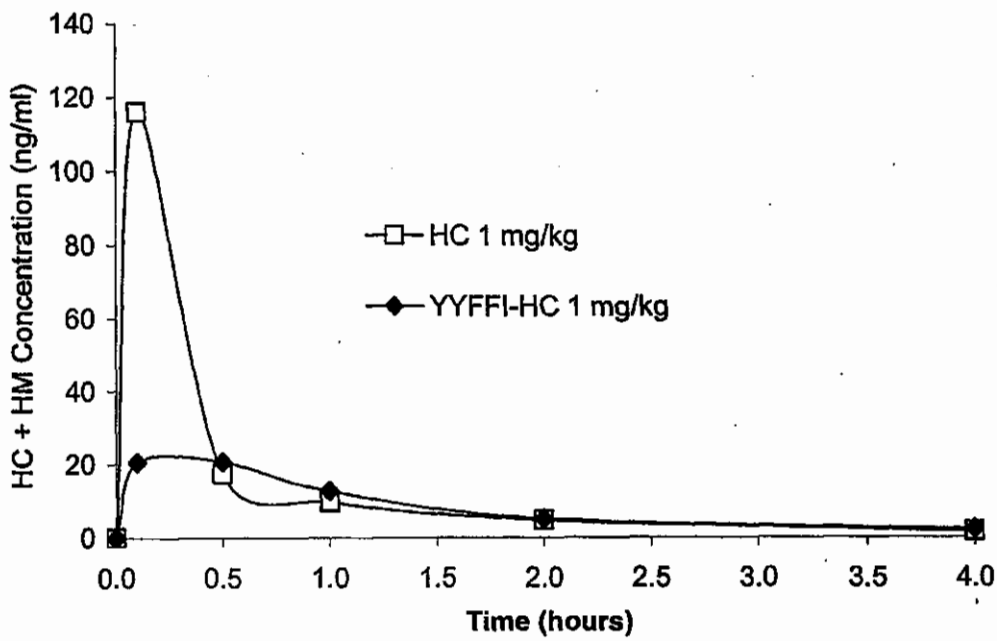

140
120
100
80
60
40
20
0
HC + HM Concentration (ng/ml)
HC 1 mg/kg
YYFFI-HC 1 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 107

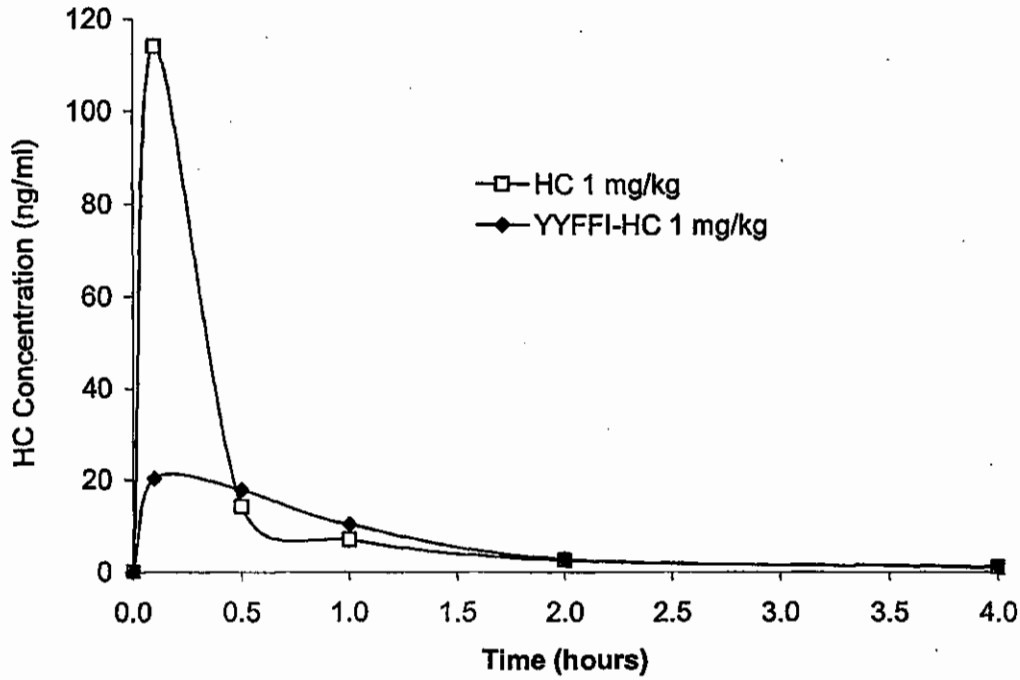

120
100
80
60
40
20
0
HC Concentration (ng/ml)
HC 1 mg/kg
YYFFI-HC 1 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 108

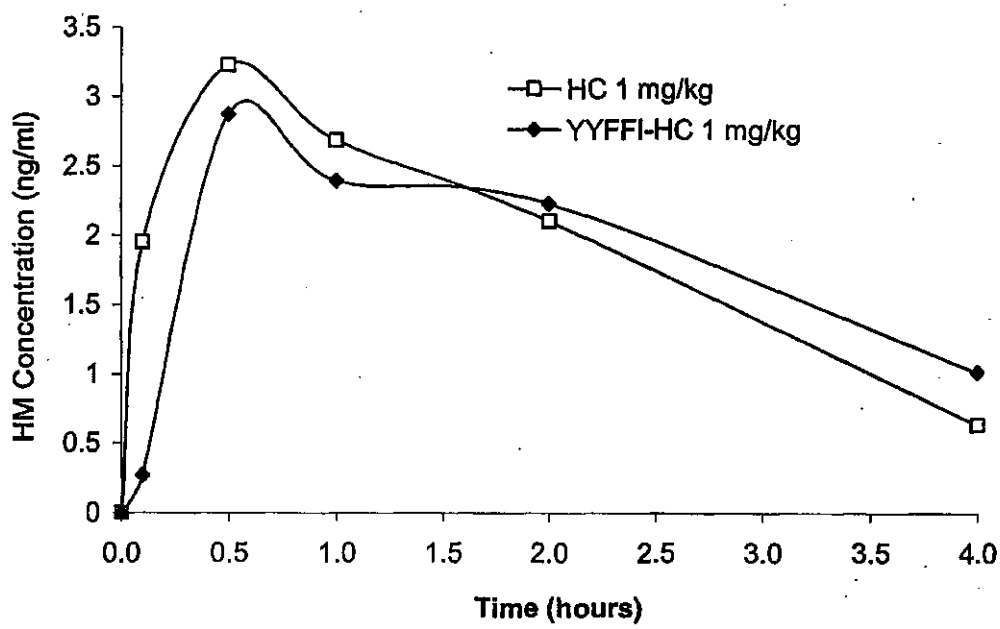

HM Concentration (ng/ml)
3.5
3
2.5
2
1.5
1
0.5
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)
HC 1 mg/kg
YYFFI-HC 1 mg/kg

Figure 109

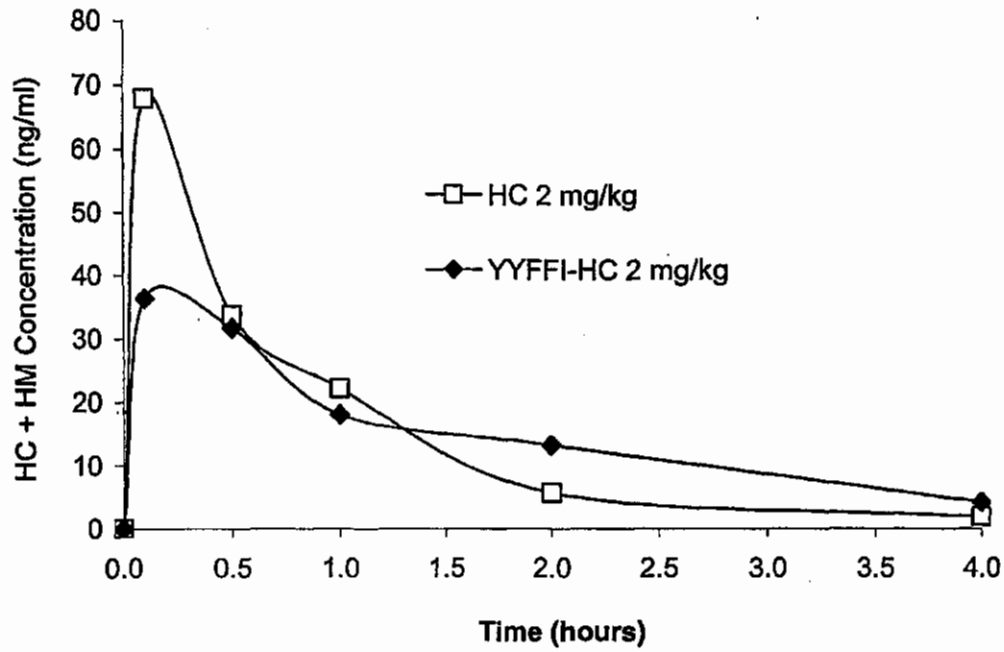

HC + HM Concentration (ng/ml)
80
70
60
50
40
30
20
10
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)
HC 2 mg/kg
YYFFI-HC 2 mg/kg

Figure 110

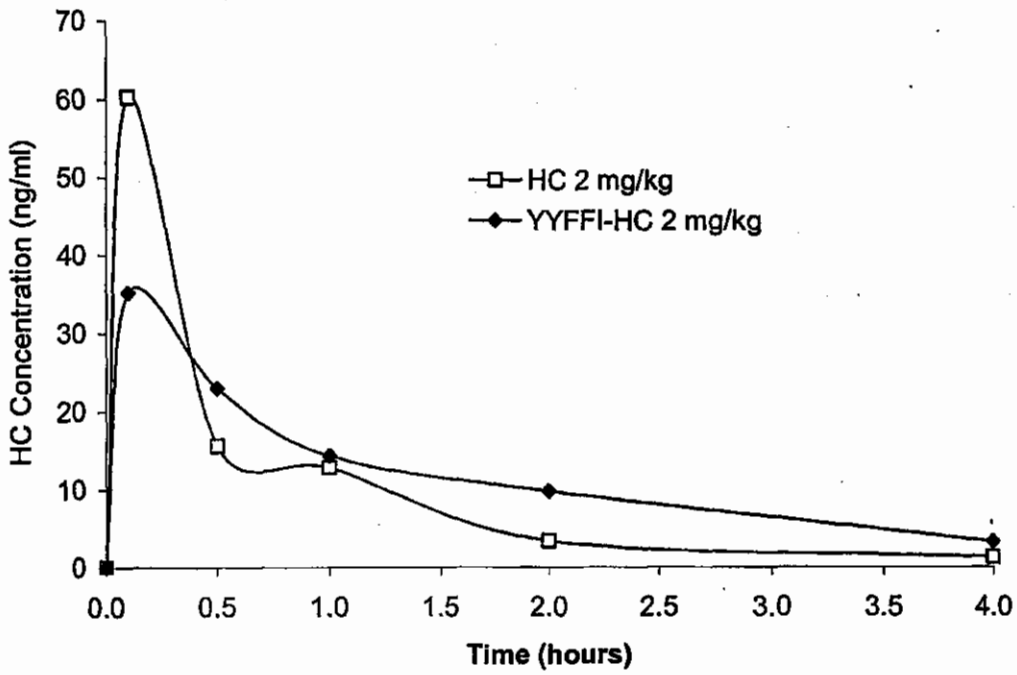

70
60
50
40
30
20
10
0
HC Concentration (ng/ml)
HC 2 mg/kg
YYFFI-HC 2 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 111

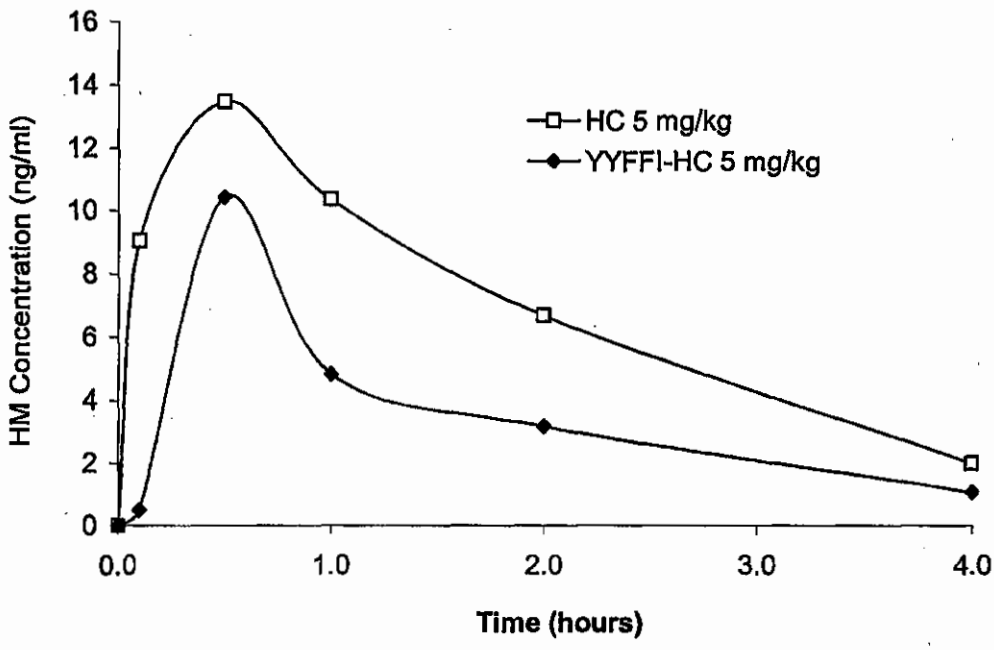

16
14
12
10
8
6
4
2
0
HM Concentration (ng/ml)
HC 5 mg/kg
YYFFI-HC 5 mg/kg
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 112

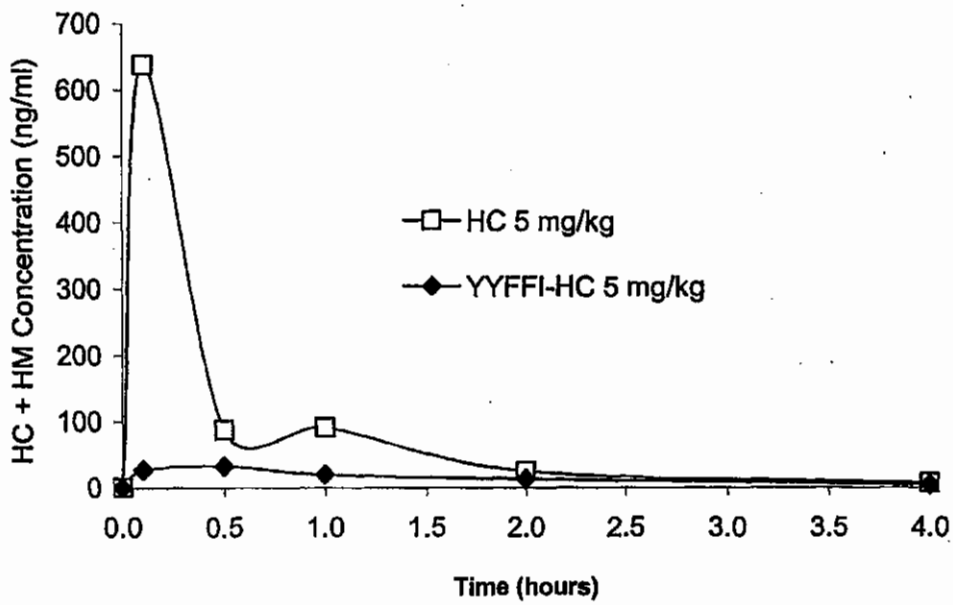

700
600
500
400
300
200
100
0
HC + HM Concentration (ng/ml)
HC 5 mg/kg
YYFFI-HC 5 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 113

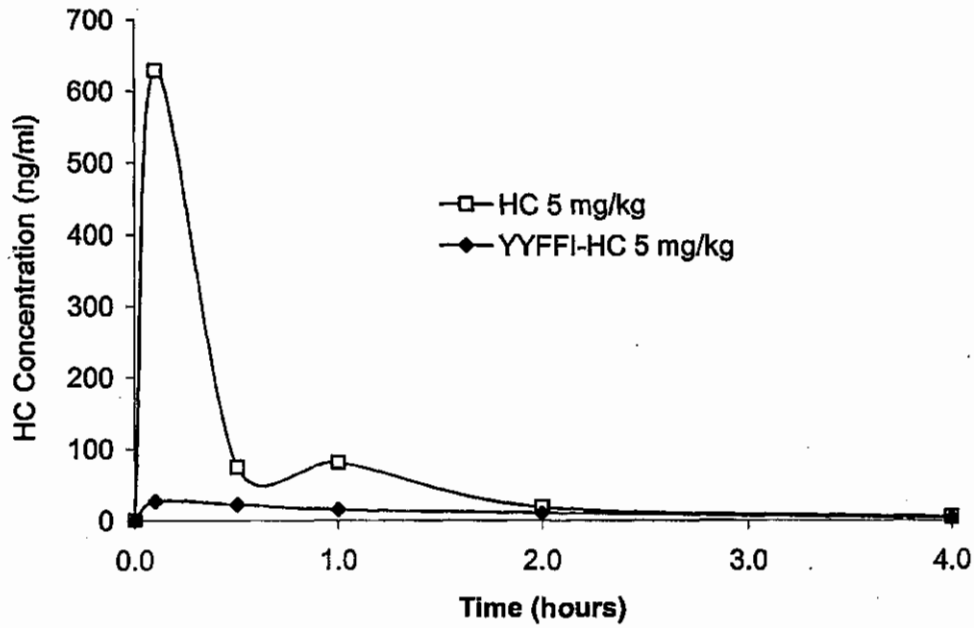

700
600
500
400
300
200
100
0
HC Concentration (ng/ml)
HC 5 mg/kg
YYFFI-HC 5 mg/kg
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 114

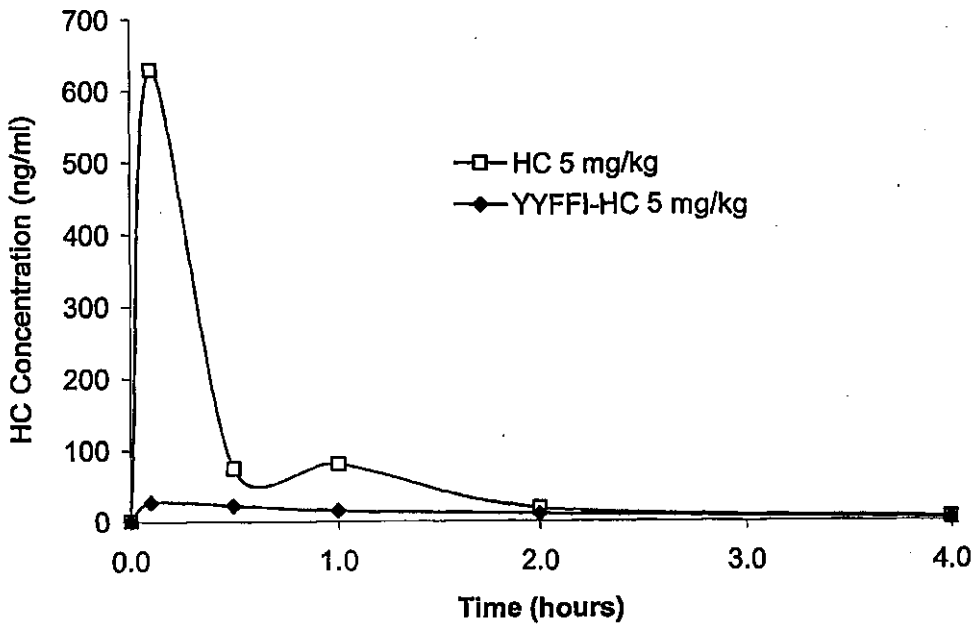

700
600
500
400
300
200
100
0
HC Concentration (ng/ml)
HC 5 mg/kg
YYFFI-HC 5 mg/kg
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 115

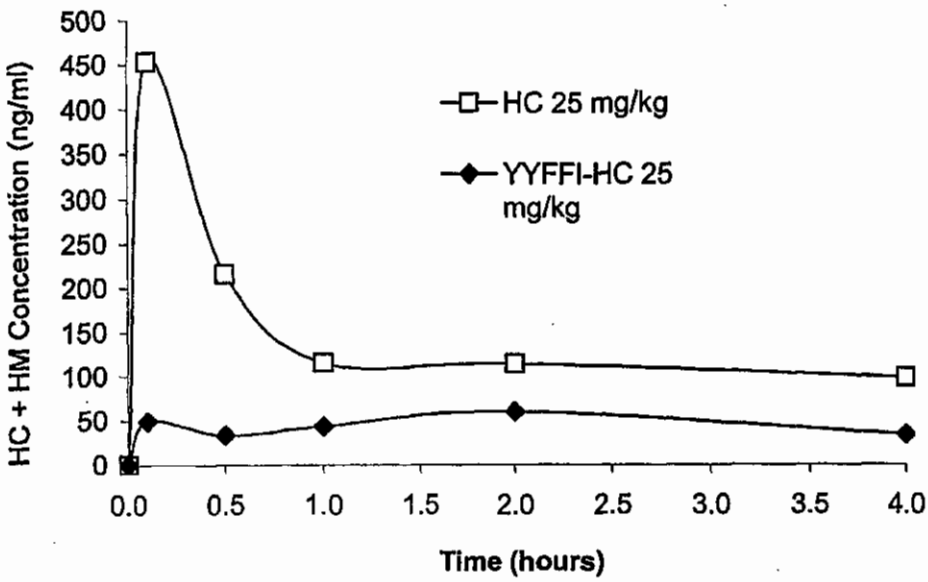

HC + HM Concentration (ng/ml)
500
450
400
350
300
250
200
150
100
50
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)
HC 25 mg/kg
YYFFI-HC 25 mg/kg

Figure 116

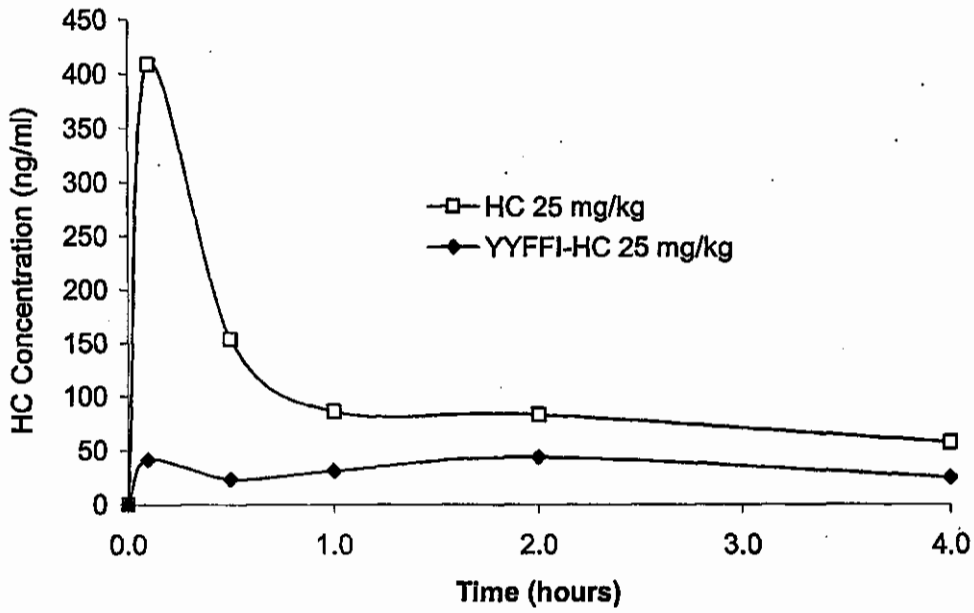

450
400
350
300
250
200
150
100
50
0
HC Concentration (ng/ml)
HC 25 mg/kg
YYFFI-HC 25 mg/kg
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 117

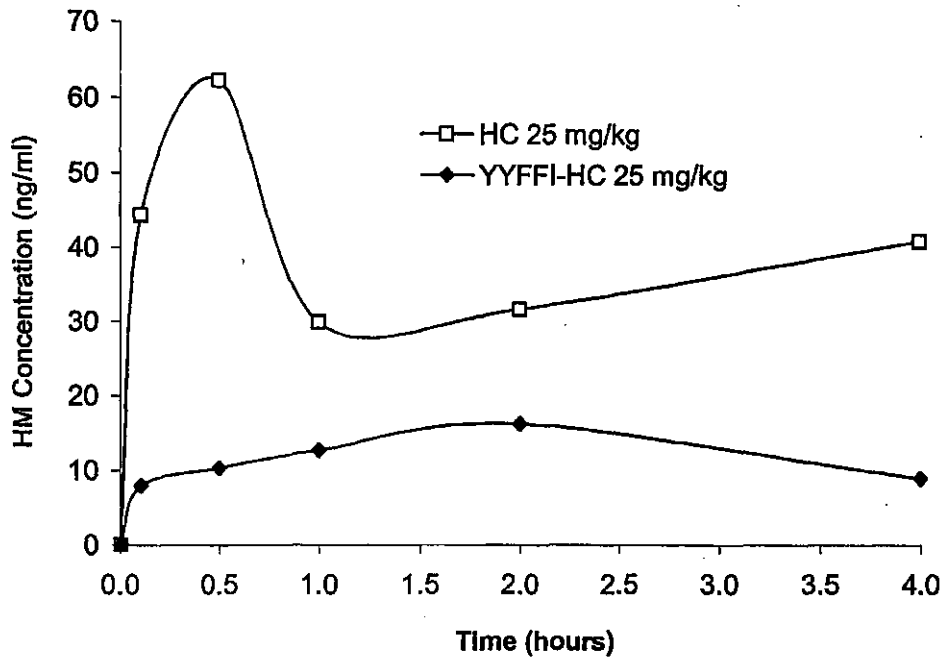

70
60
50
40
30
20
10
0
HM Concentration (ng/ml)
HC 25 mg/kg
YYFFI-HC 25 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 118

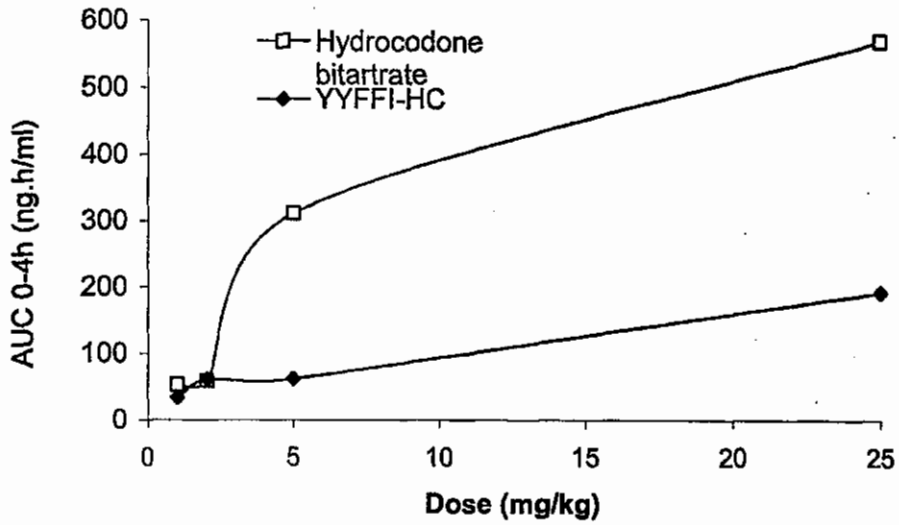

600
500
400
300
200
100
0
AUC 0-4h (ng.h/ml)
Hydrocodone bitartrate
YYFFI-HC
0
5
10
15
20
25
Dose (mg/kg)

Figure 119

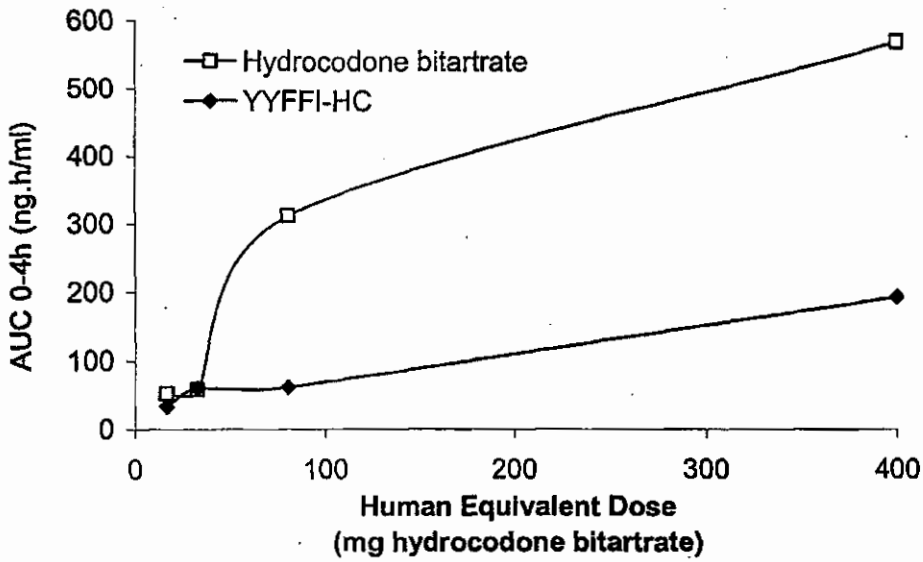

600
500
400
300
200
100
0
AUC 0-4h (ng.h/ml)
Hydrocodone bitartrate
YYFFI-HC
0
100
200
300
400
Human Equivalent Dose
(mg hydrocodone bitartrate)

Figure 120

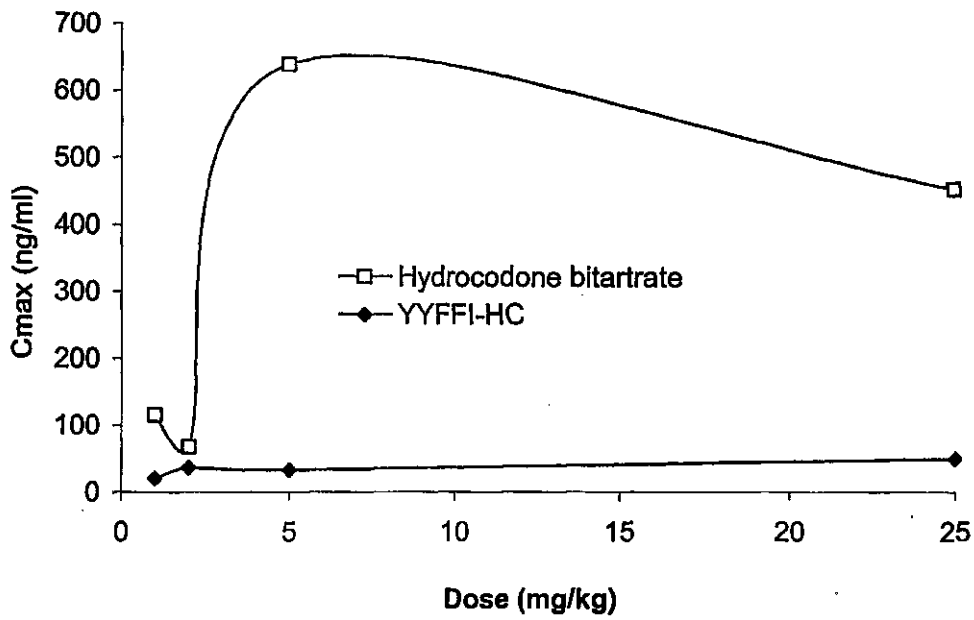

700
600
500
400
300
200
100
0
Cmax (ng/ml)
0
5
10
15
20
25
Dose (mg/kg)
Hydrocodone bitartrate
YYFFI-HC

Figure 121

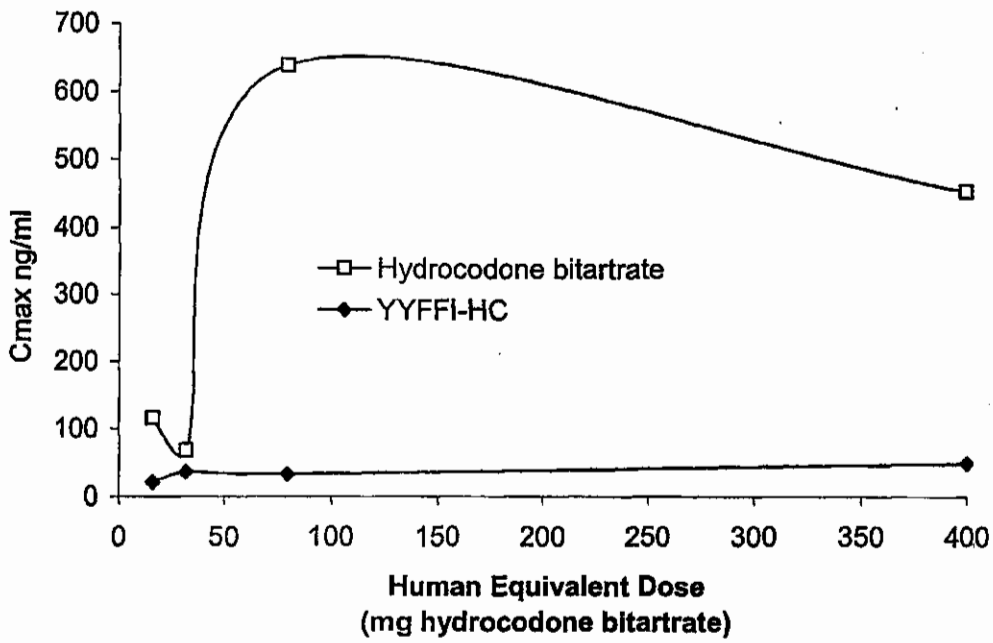

700
600
500
400
300
200
100
0
Cmax ng/ml
Hydrocodone bitartrate
YYFFI-HC
0
50
100
150
200
250
300
350
400
Human Equivalent Dose
(mg hydrocodone bitartrate)

Figure 122

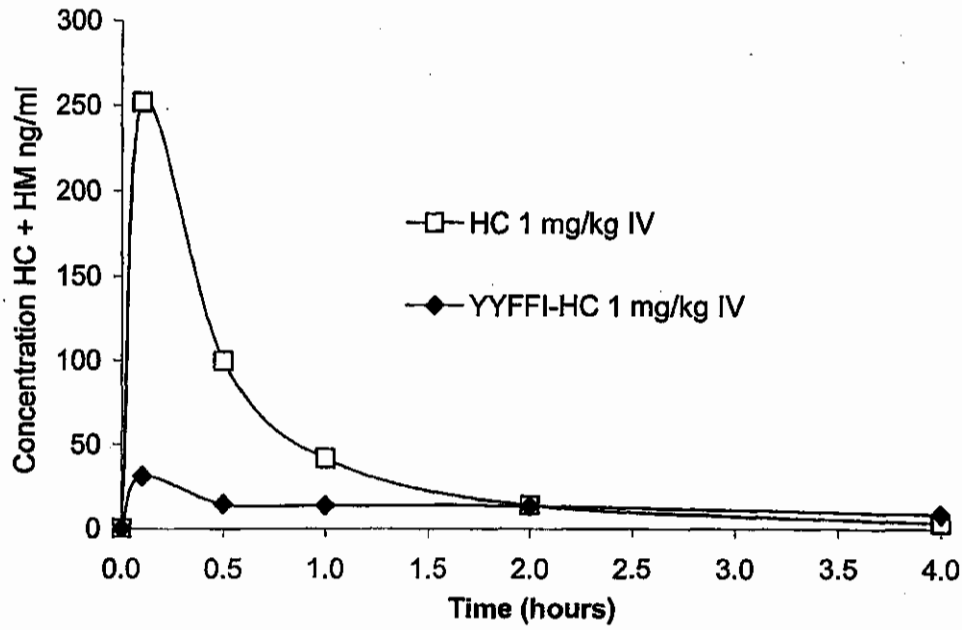

300
250
200
150
100
50
0
Concentration HC + HM ng/ml
HC 1 mg/kg IV
YYFFI-HC 1 mg/kg IV
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 123

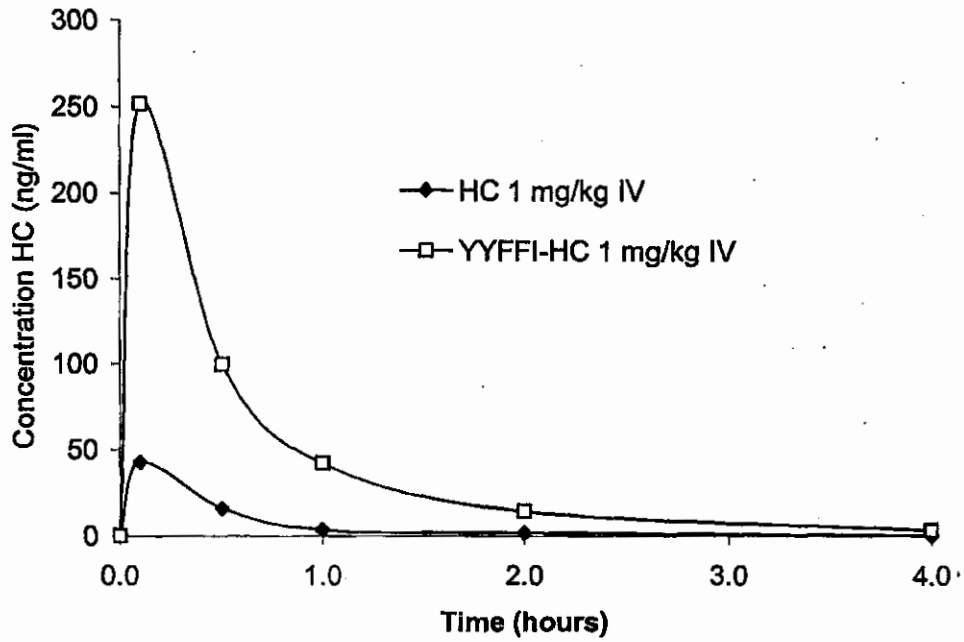

300
250
200
150
100
50
0
Concentration HC (ng/ml)
HC 1 mg/kg IV
YYFFI-HC 1 mg/kg IV
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 124

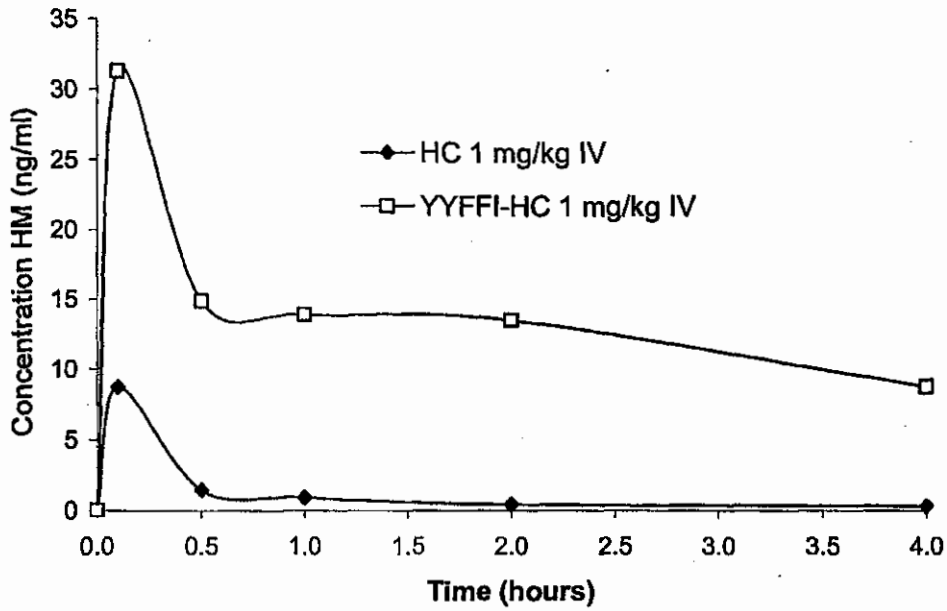

35
30
25
20
15
10
5
0
Concentration HM (ng/ml)
HC 1 mg/kg IV
YYFFI-HC 1 mg/kg IV
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 125

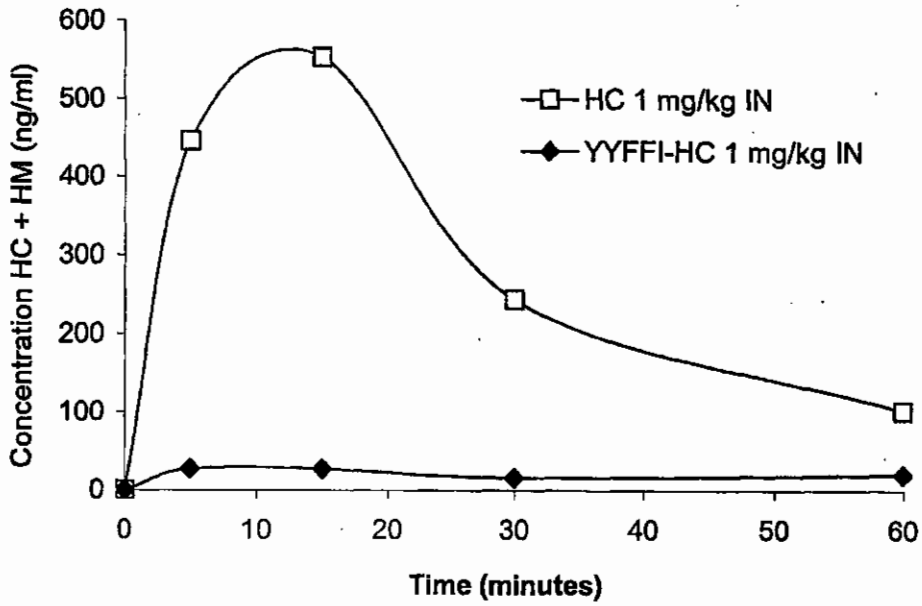

600
500
400
300
200
100
0
Concentration HC + HM (ng/ml)
0
10
20
30
40
50
60
Time (minutes)
HC 1 mg/kg IN
YYFFI-HC 1 mg/kg IN

Figure 126

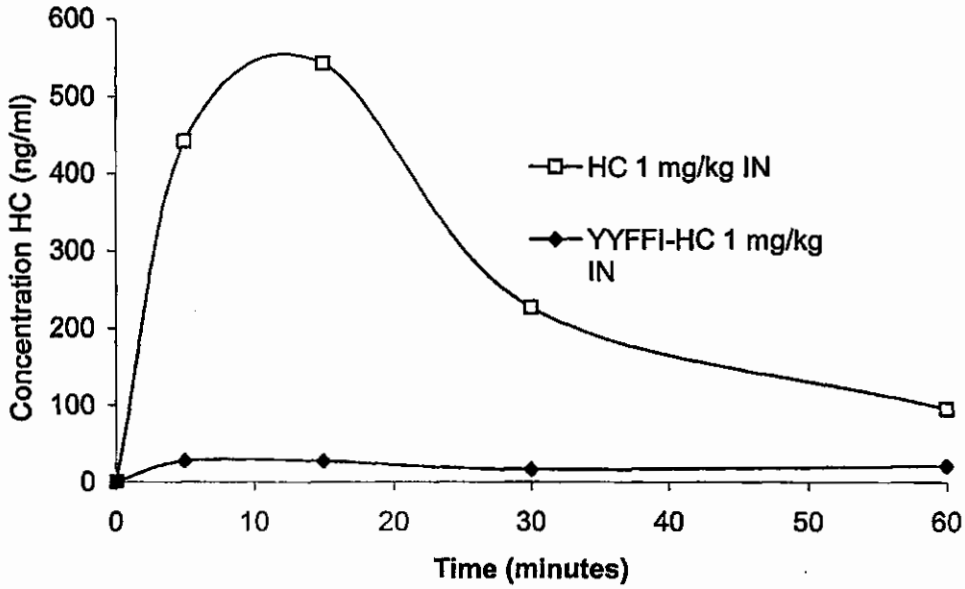

600
500
400
300
200
100
0
Concentration HC (ng/ml)
0
10
20
30
40
50
60
Time (minutes)
HC 1 mg/kg IN
YYFFI-HC 1 mg/kg IN

Figure 127

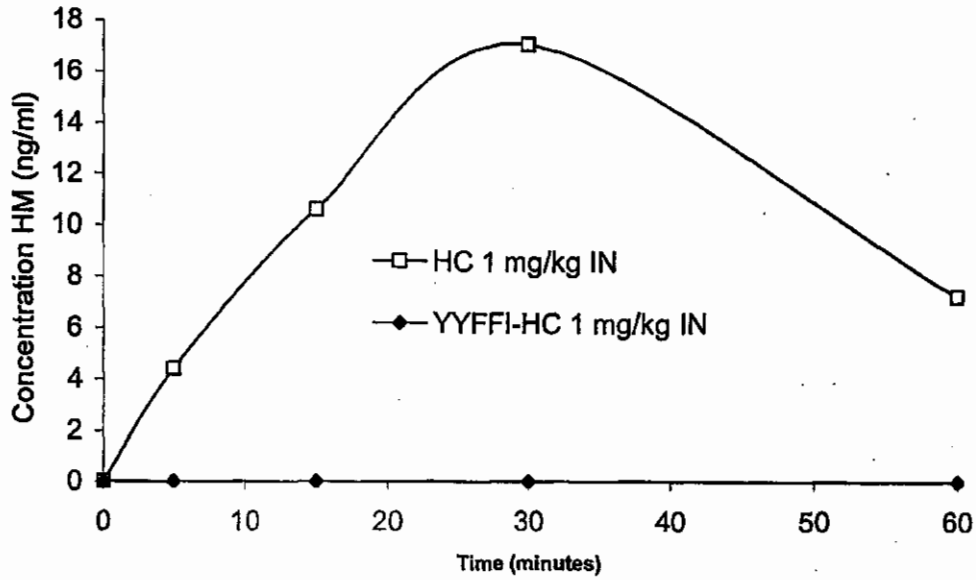

Concentration HM (ng/ml)
18
16
14
12
10
8
6
4
2
0
0
10
20
30
40
50
60
Time (minutes)
HC 1 mg/kg IN
YYFFI-HC 1 mg/kg IN

Figure 128

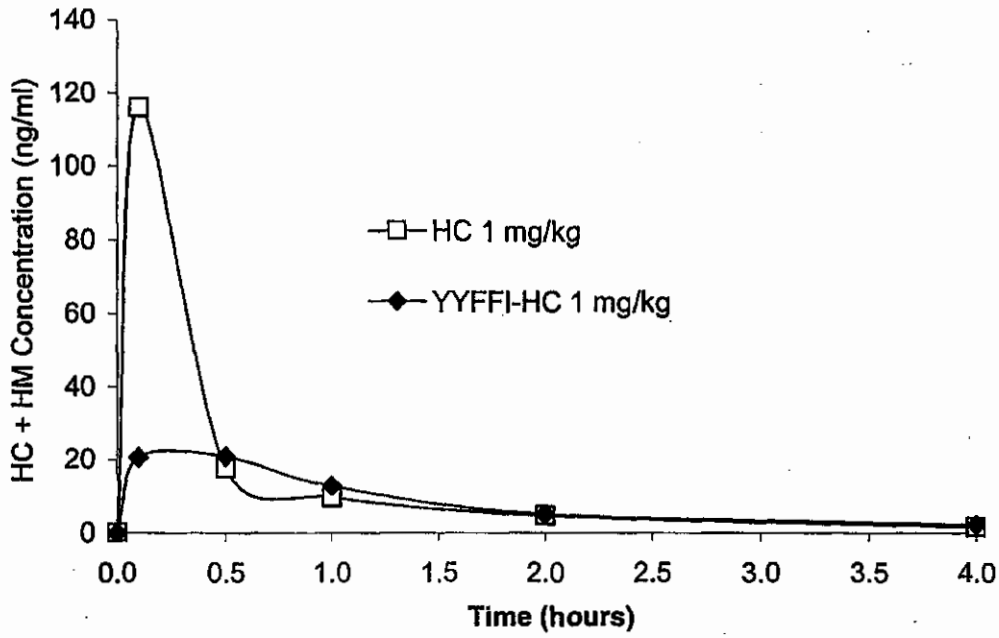

140
120
100
80
60
40
20
0
HC + HM Concentration (ng/ml)
HC 1 mg/kg
YYFFI-HC 1 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 129

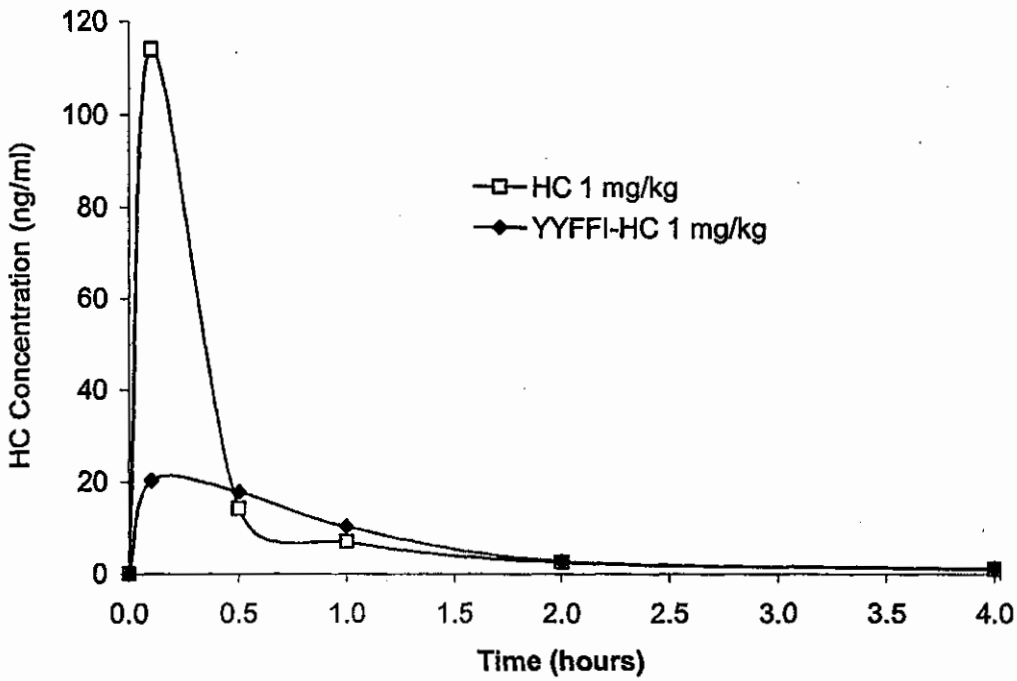

120
100
80
60
40
20
0
HC Concentration (ng/ml)
HC 1 mg/kg
YYFFI-HC 1 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 130

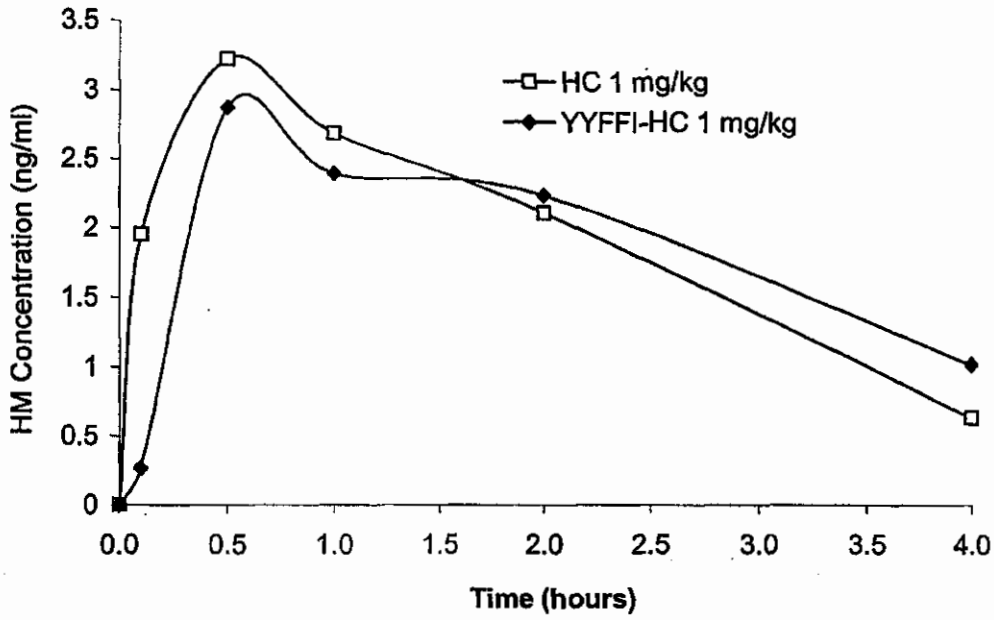

3.5
3
2.5
2
1.5
1
0.5
0
HM Concentration (ng/ml)
HC 1 mg/kg
YYFFI-HC 1 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 131

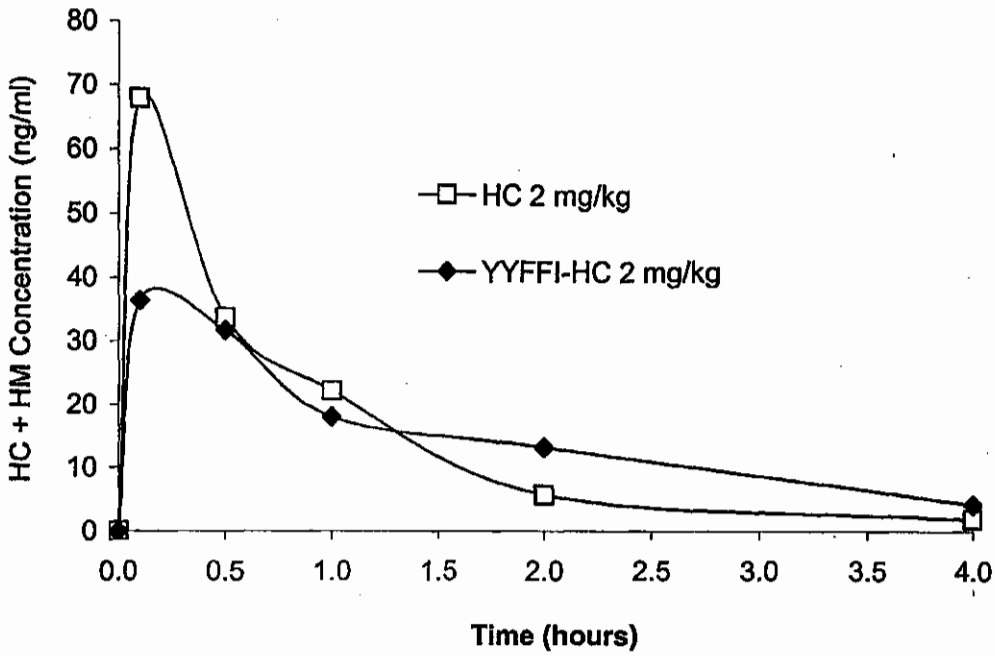

HC + HM Concentration (ng/ml)
80
70
60
50
40
30
20
10
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)
HC 2 mg/kg
YYFFI-HC 2 mg/kg

Figure 132

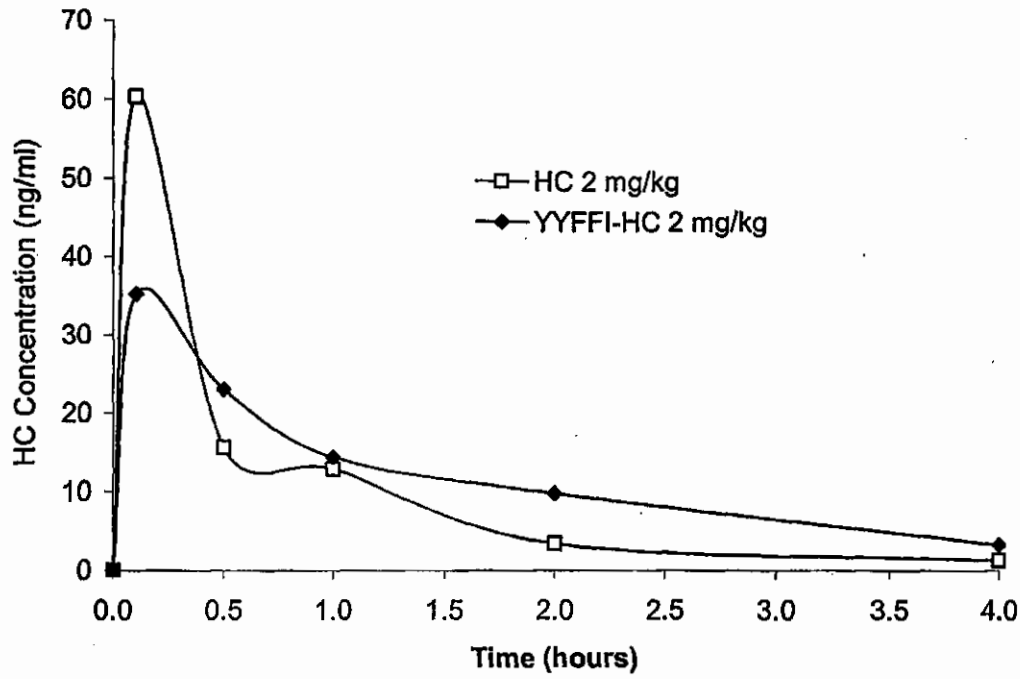

70
60
50
40
30
20
10
0
HC Concentration (ng/ml)
HC 2 mg/kg
YYFFI-HC 2 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 133

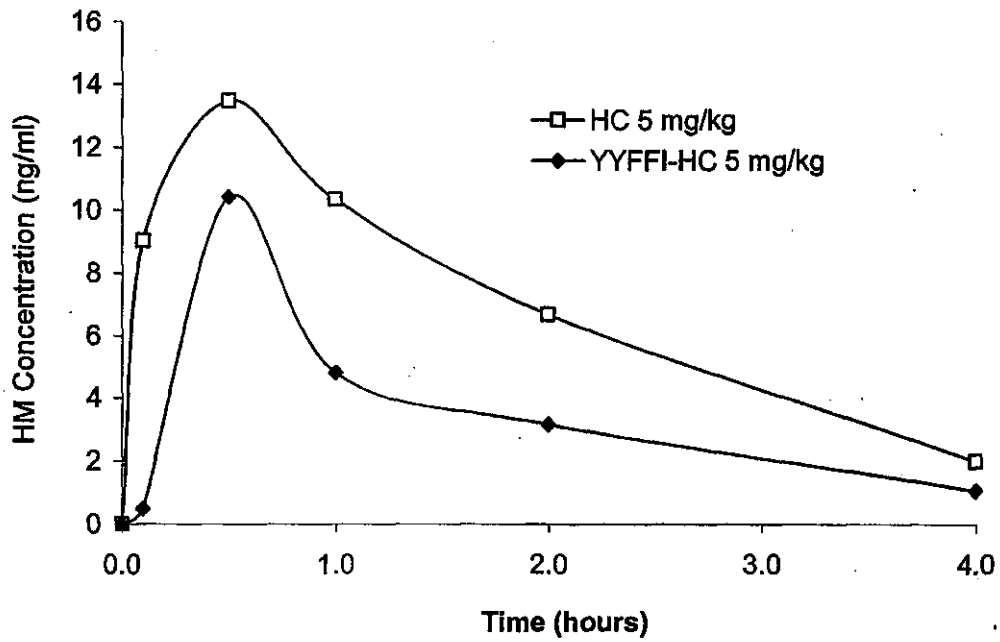

16
14
12
10
8
6
4
2
0
HM Concentration (ng/ml)
HC 5 mg/kg
YYFFI-HC 5 mg/kg
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 134

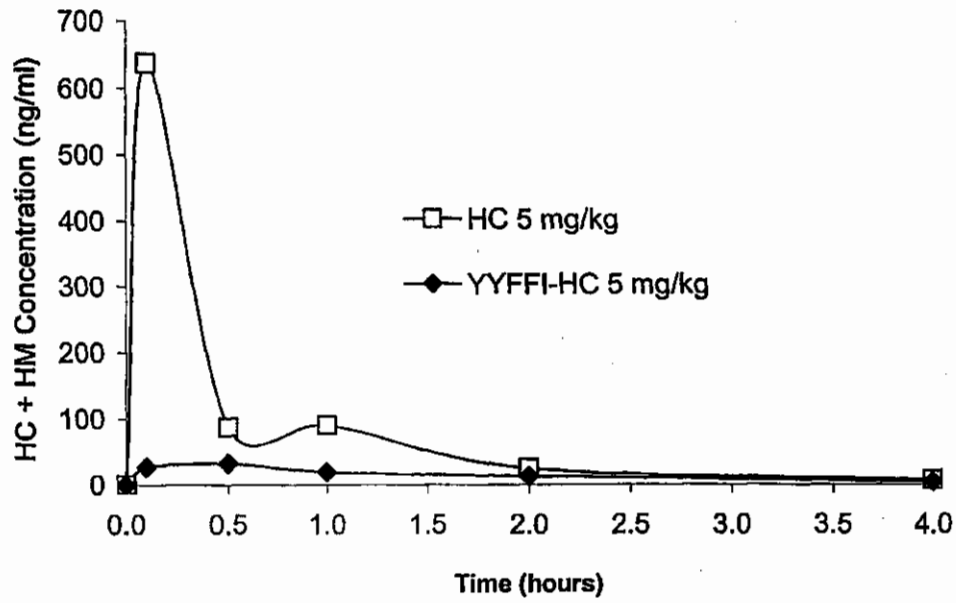

HC + HM Concentration (ng/ml)
700
600
500
400
300
200
100
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)
HC 5 mg/kg
YYFFI-HC 5 mg/kg

Figure 135

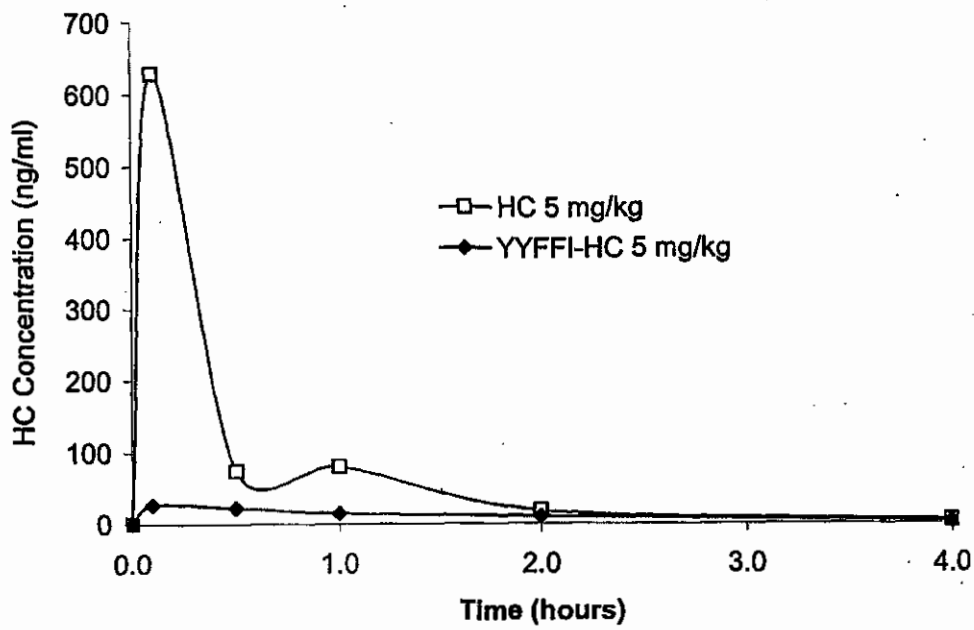

700
600
500
400
300
200
100
0
HC Concentration (ng/ml)
HC 5 mg/kg
YYFFI-HC 5 mg/kg
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 136

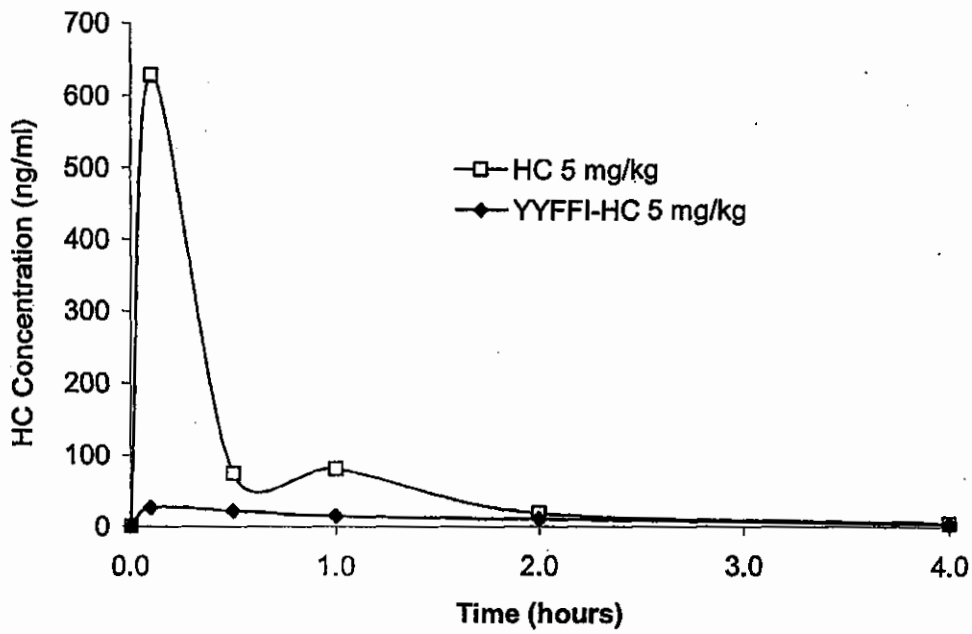

700
600
500
400
300
200
100
0
HC Concentration (ng/ml)
HC 5 mg/kg
YYFFI-HC 5 mg/kg
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 137

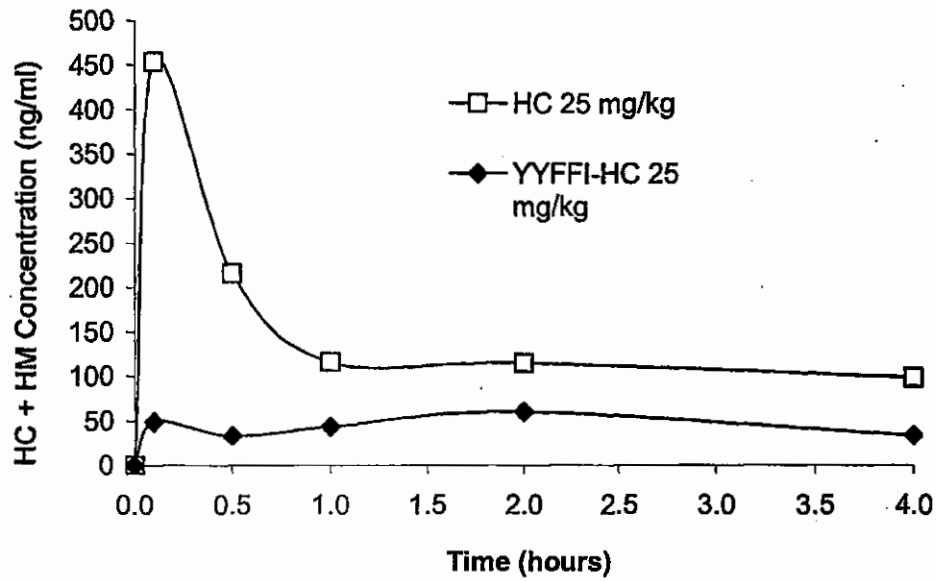

HC + HM Concentration (ng/ml)
500
450
400
350
300
250
200
150
100
50
0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)
HC 25 mg/kg
YYFFI-HC 25 mg/kg

Figure 138

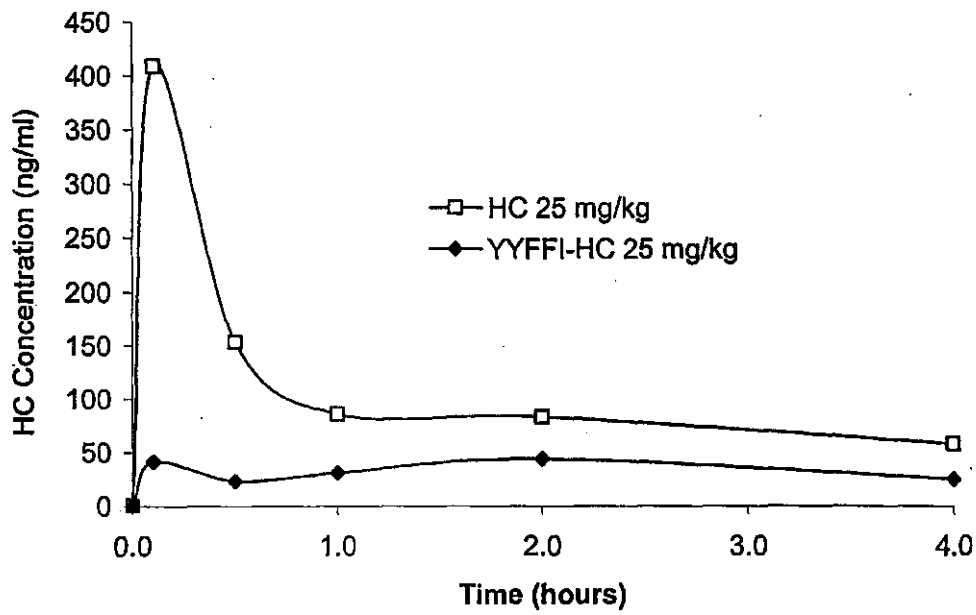

HC Concentration (ng/ml)
450
400
350
300
250
200
150
100
50
0
0.0
1.0
2.0
3.0
4.0
Time (hours)
HC 25 mg/kg
YYFFI-HC 25 mg/kg

Figure 139

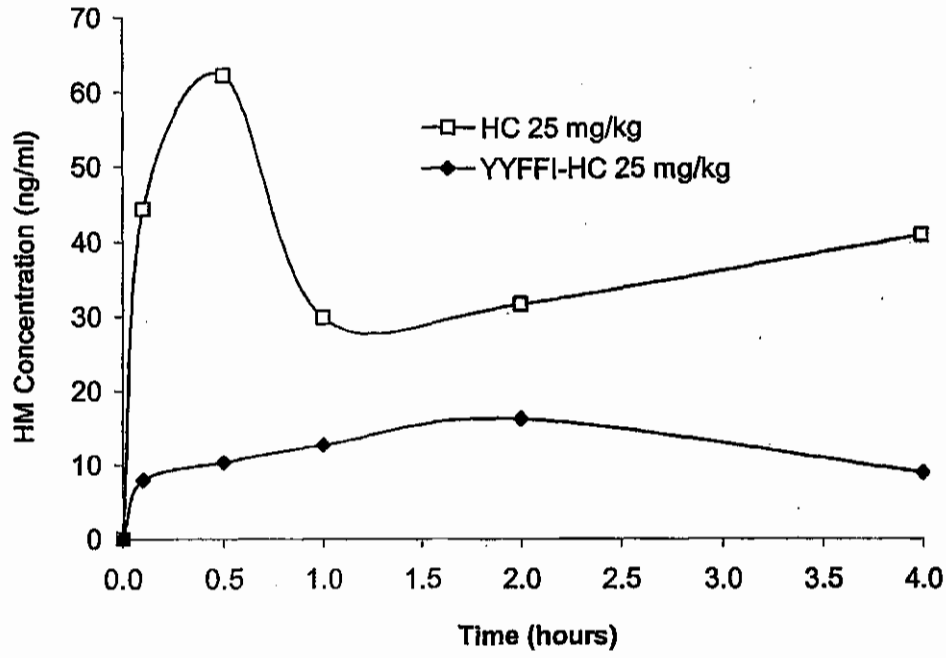

70
60
50
40
30
20
10
0
HM Concentration (ng/ml)
HC 25 mg/kg
YYFFI-HC 25 mg/kg
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 140

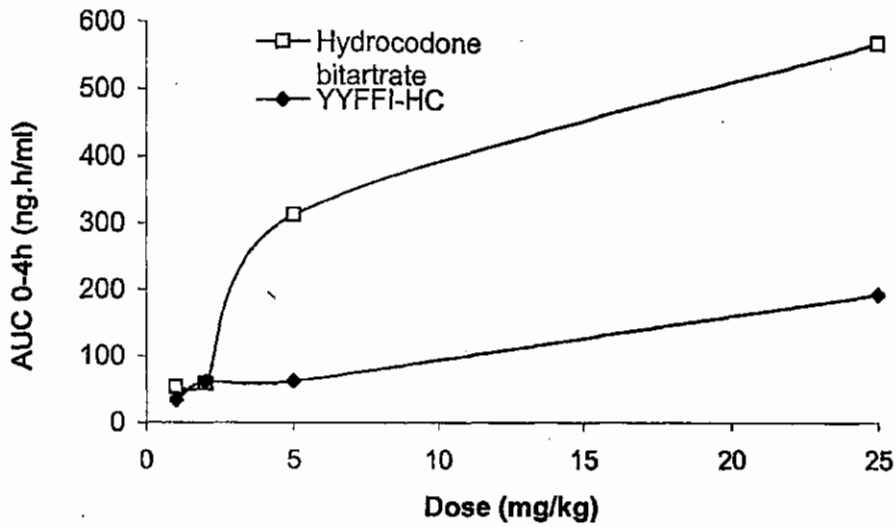

600
500
400
300
200
100
0
AUC 0-4h (ng.h/ml)
Hydrocodone bitartrate
YYFFI-HC
0
5
10
15
20
25
Dose (mg/kg)

Figure 141

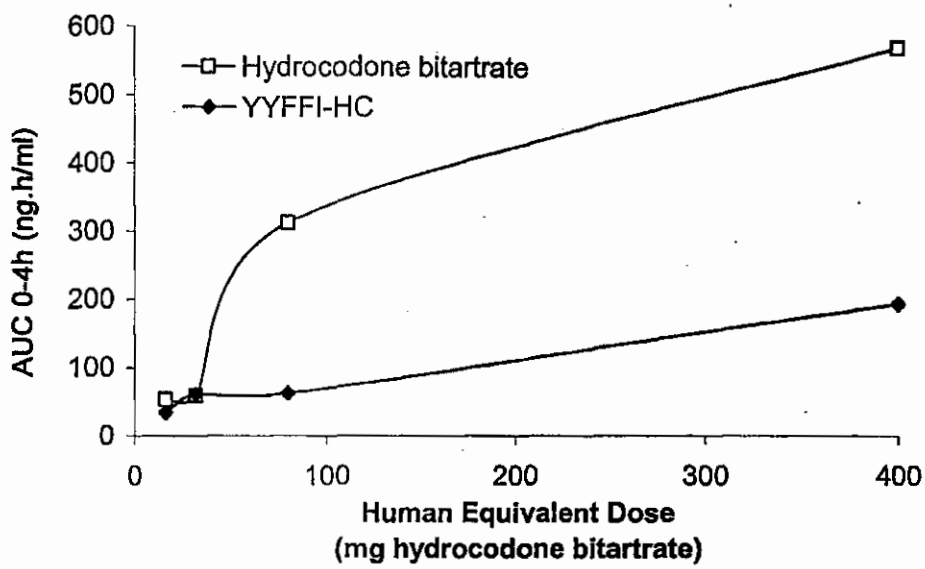

600
500
400
300
200
100
0
AUC 0-4h (ng.h/ml)
Hydrocodone bitartrate
YYFFI-HC
0
100
200
300
400
Human Equivalent Dose
(mg hydrocodone bitartrate)

Figure 142

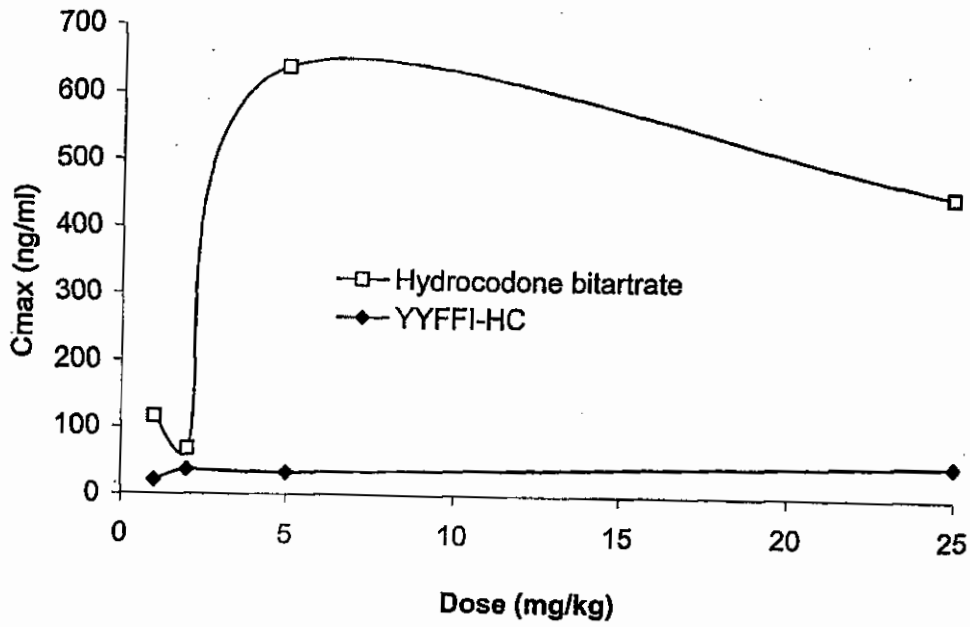

700
600
500
400
300
200
100
0
Cmax (ng/ml)
Hydrocodone bitartrate
YYFFI-HC
0
5
10
15
20
25
Dose (mg/kg)

Figure 143

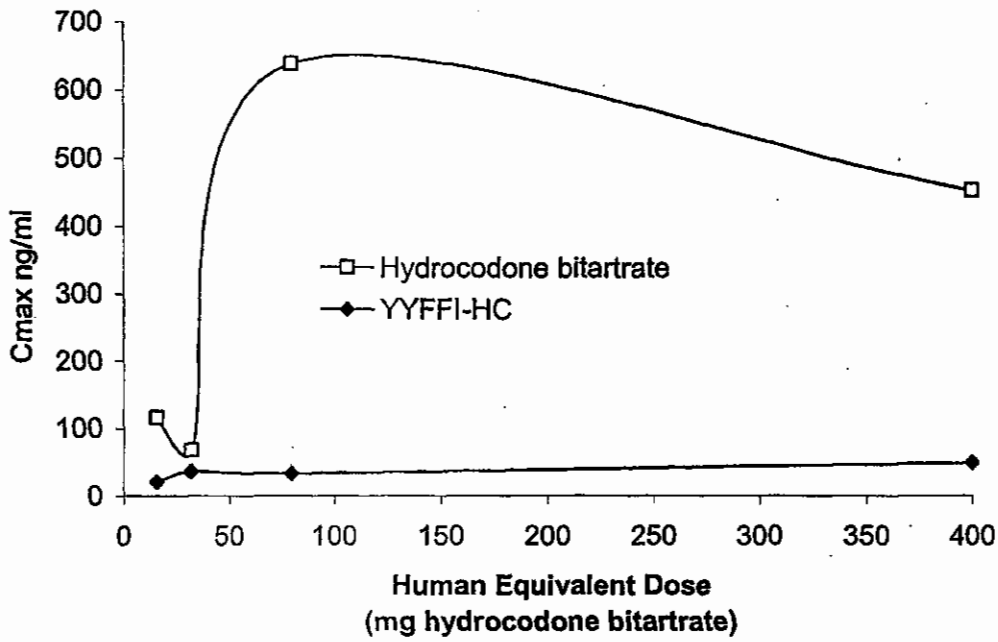

700
600
500
400
300
200
100
0
Cmax ng/ml
Hydrocodone bitartrate
YYFFI-HC
0
50
100
150
200
250
300
350
400
Human Equivalent Dose
(mg hydrocodone bitartrate)

Figure 144

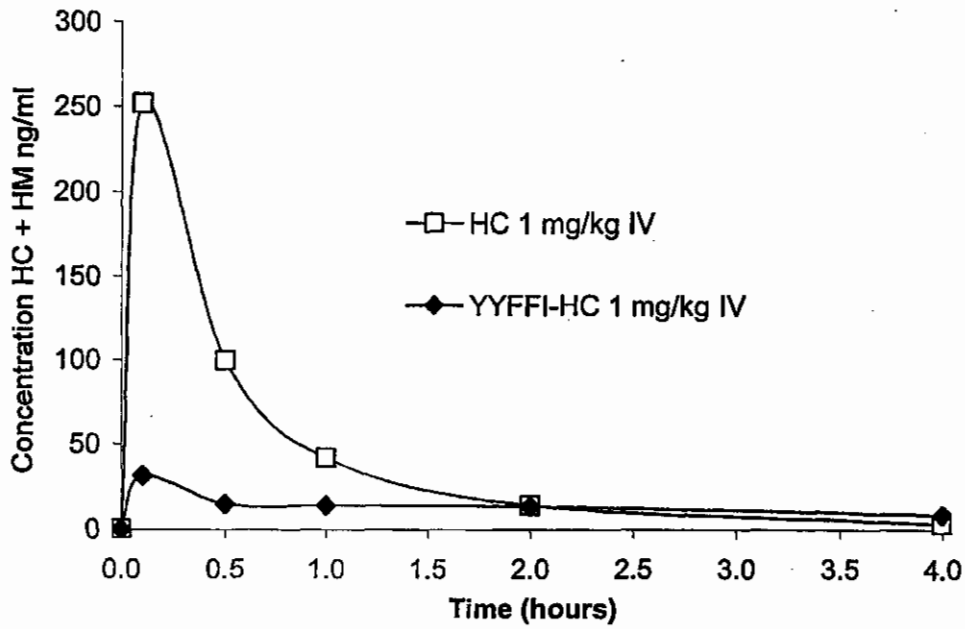

300
250
200
150
100
50
0
Concentration HC + HM ng/ml
HC 1 mg/kg IV
YYFFI-HC 1 mg/kg IV
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 145

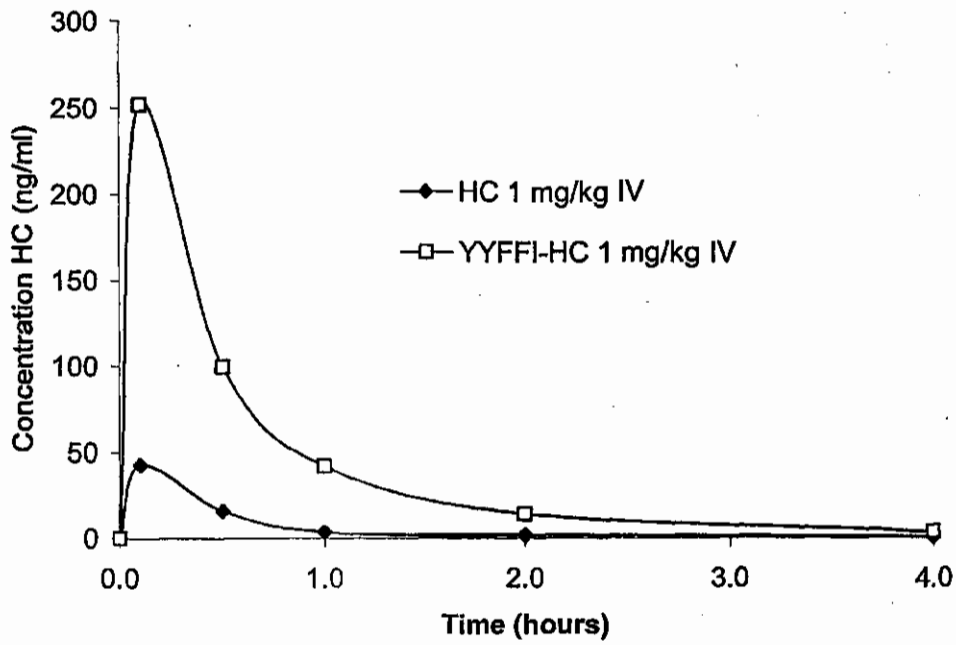

300
250
200
150
100
50
0
Concentration HC (ng/ml)
HC 1 mg/kg IV
YYFFI-HC 1 mg/kg IV
0.0
1.0
2.0
3.0
4.0
Time (hours)

Figure 146

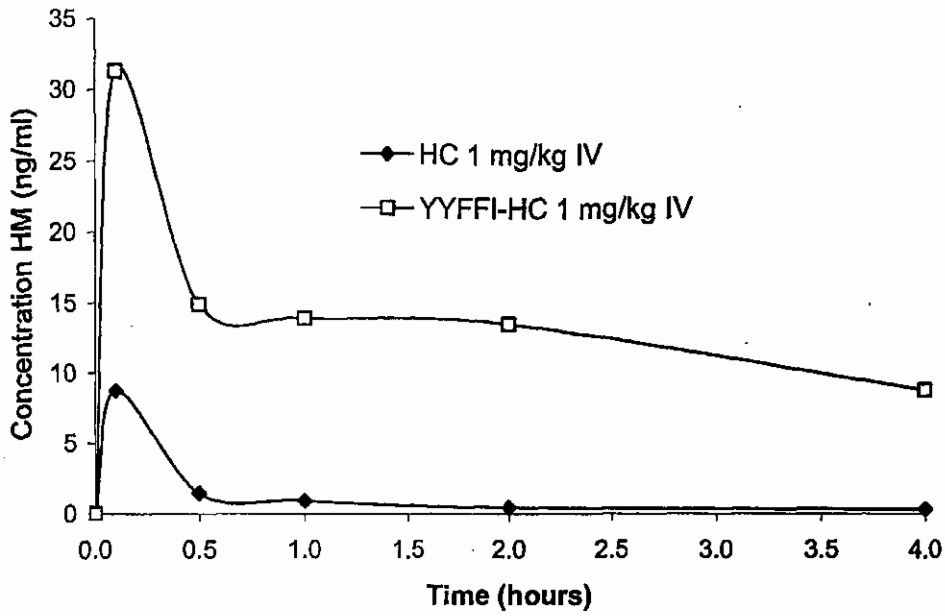

35
30
25
20
15
10
5
0
Concentration HM (ng/ml)
HC 1 mg/kg IV
YYFFI-HC 1 mg/kg IV
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
Time (hours)

Figure 147

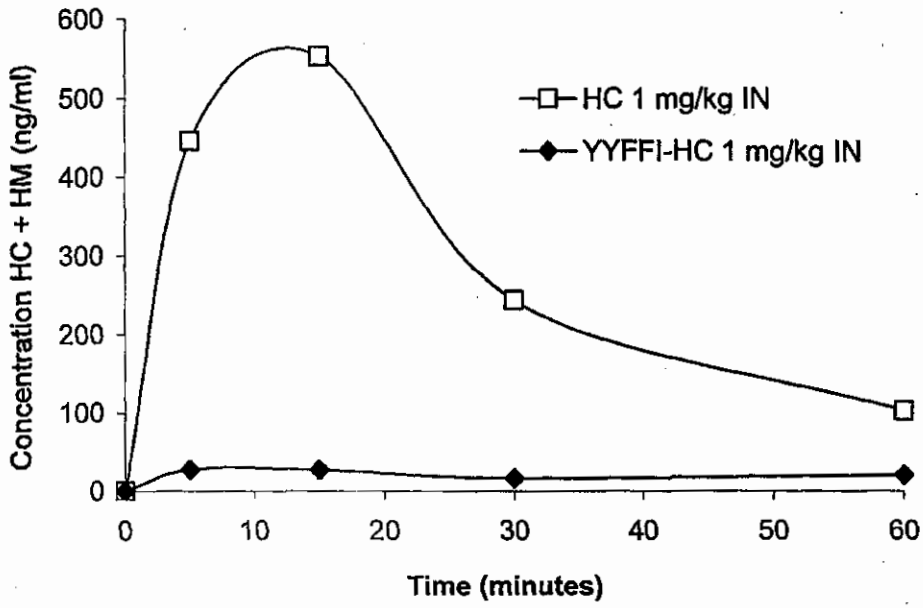

600
500
400
300
200
100
0
Concentration HC + HM (ng/ml)
0
10
20
30
40
50
60
Time (minutes)
HC 1 mg/kg IN
YYFFI-HC 1 mg/kg IN

Figure 148

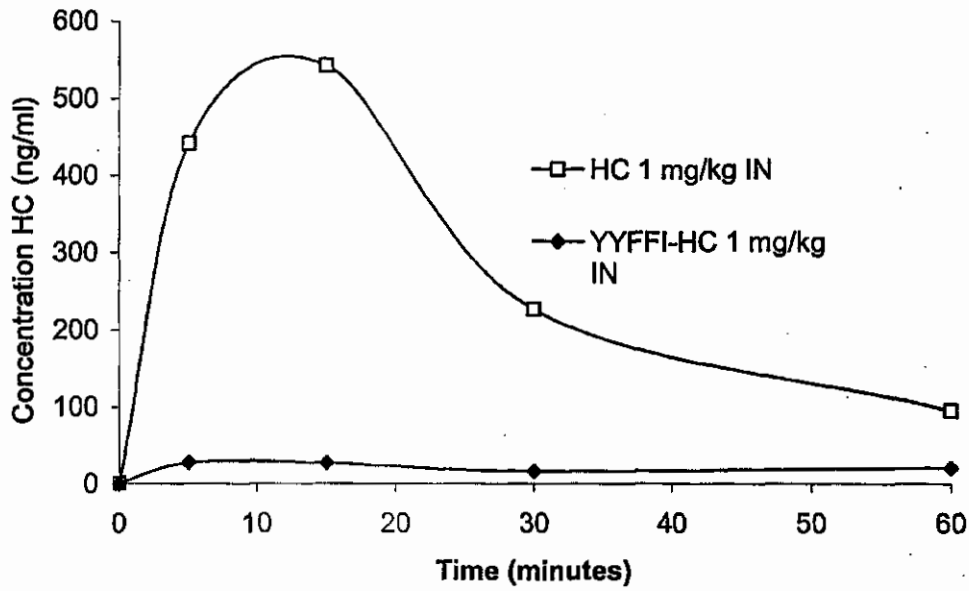

600
500
400
300
200
100
0
Concentration HC (ng/ml)
0
10
20
30
40
50
60
Time (minutes)
HC 1 mg/kg IN
YYFFI-HC 1 mg/kg IN

Figure 149

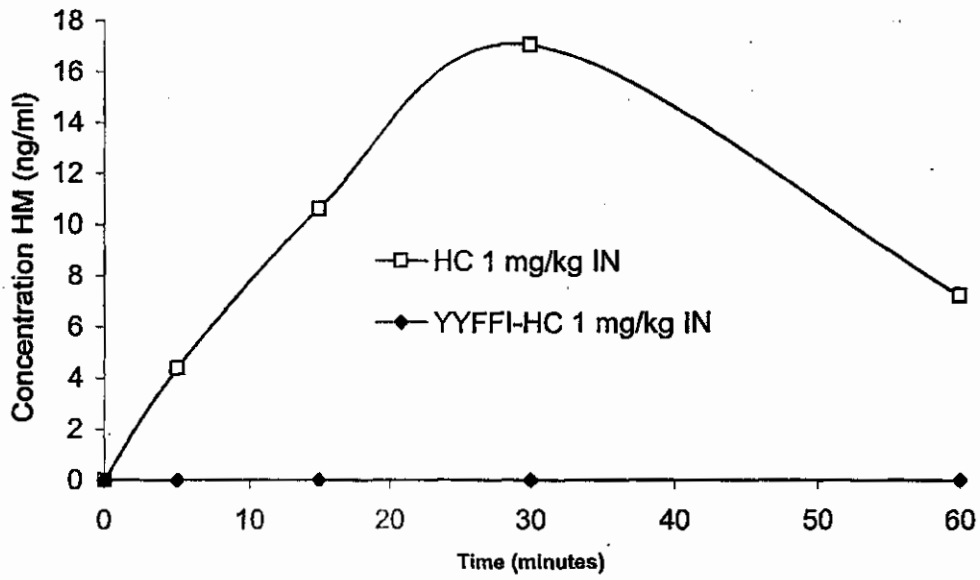

Concentration HM (ng/ml)
18
16
14
12
10
8
6
4
2
0
0
10
20
30
40
50
60
Time (minutes)
HC 1 mg/kg IN
YYFFI-HC 1 mg/kg IN

Figure 150

Figure 151

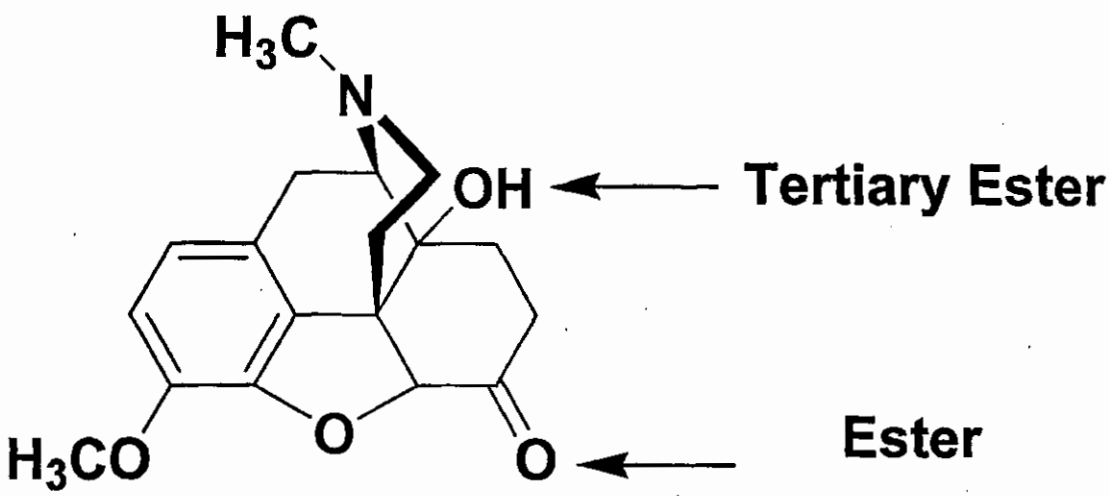


Figure 152

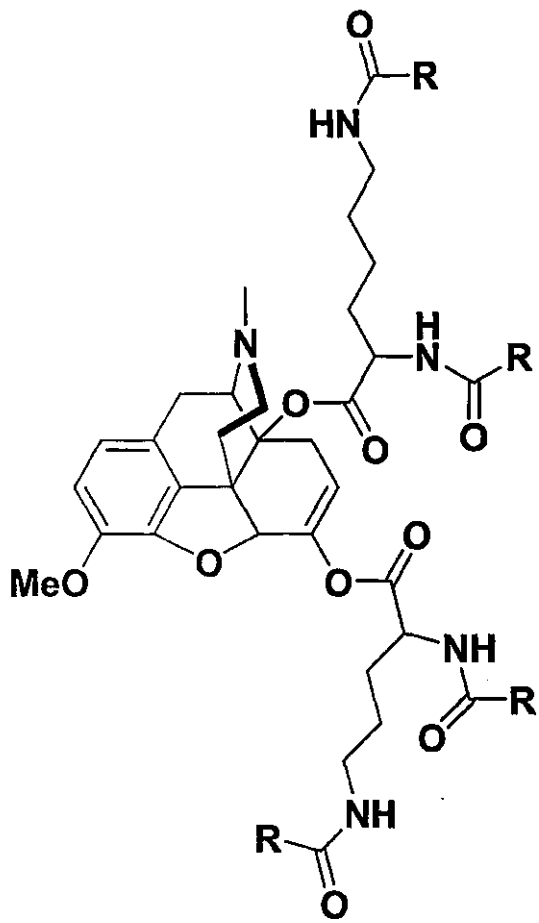


Figure 153

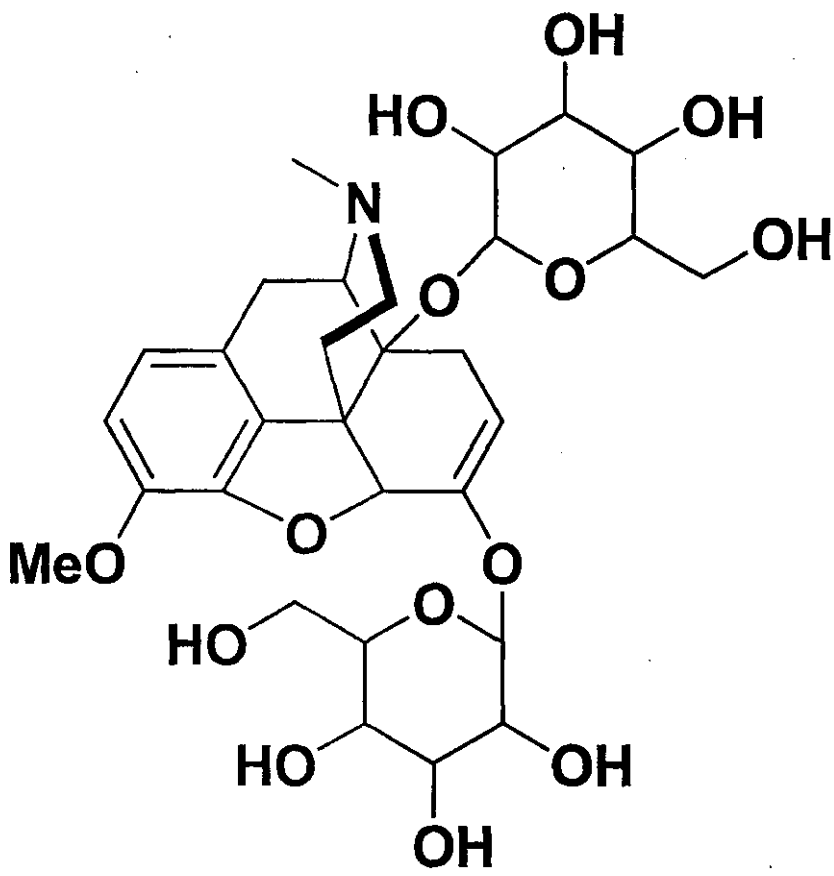


Figure 154

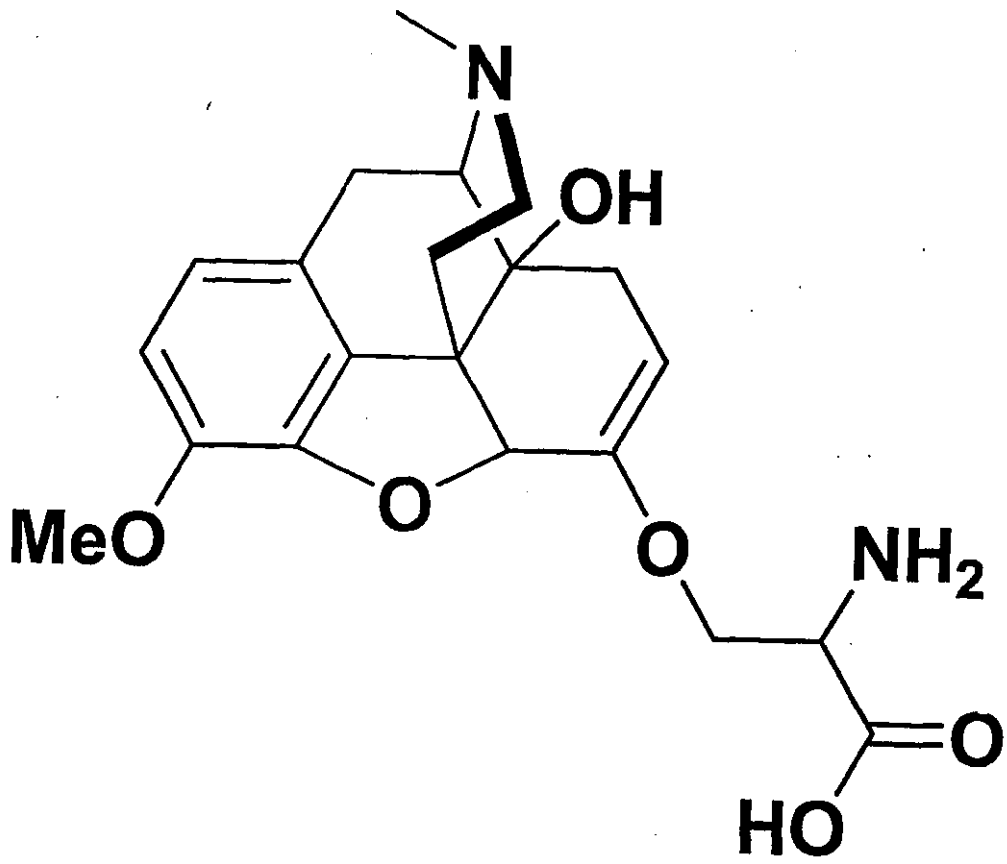
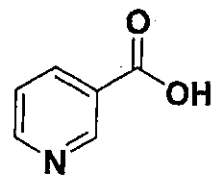
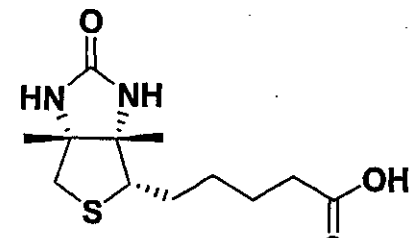


Figure 155



Niacin



Biotin

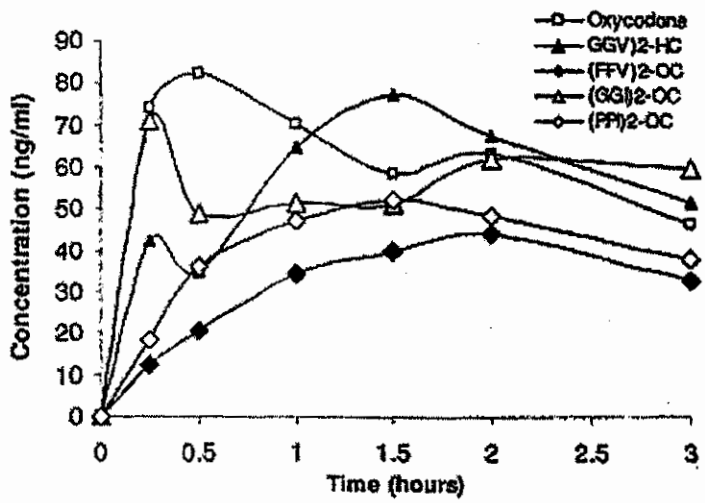

Oxycodone
GGV)2-HC
(FFV)2-OC
(GGI)2-OC
(PPI)2-OC
Concentration (ng/ml)
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
Time (hours)

Figure 156

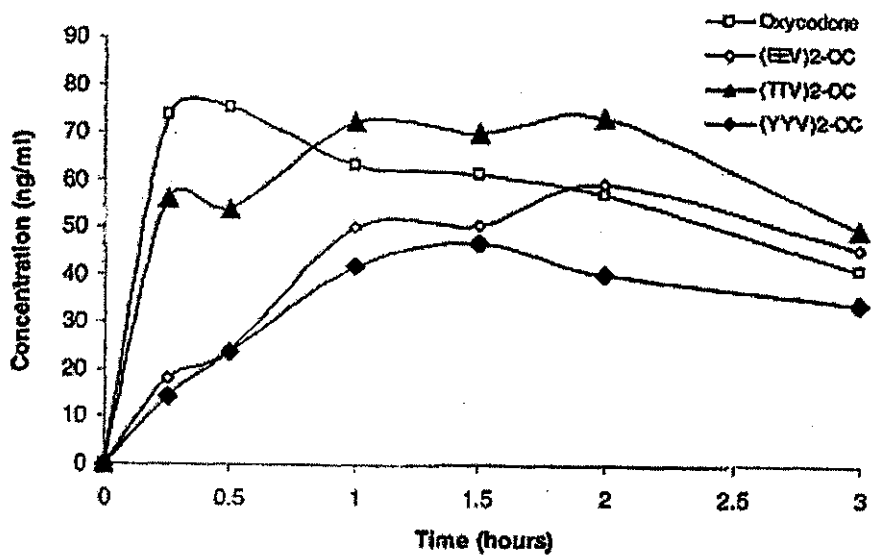

Oxycodone
(EEV)2-OC
(TTV)2-OC
(YYV)2-OC
Concentration (ng/ml)
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
Time (hours)

Figure 157

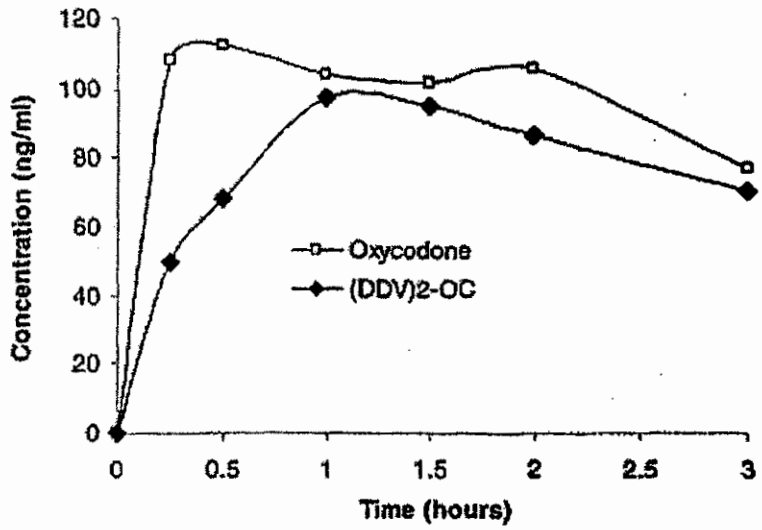

120
100
80
60
40
20
0
Concentration (ng/ml)
0
0.5
1
1.5
2
2.5
3
Time (hours)
Oxycodone
(DDV)2-OC

Figure 158

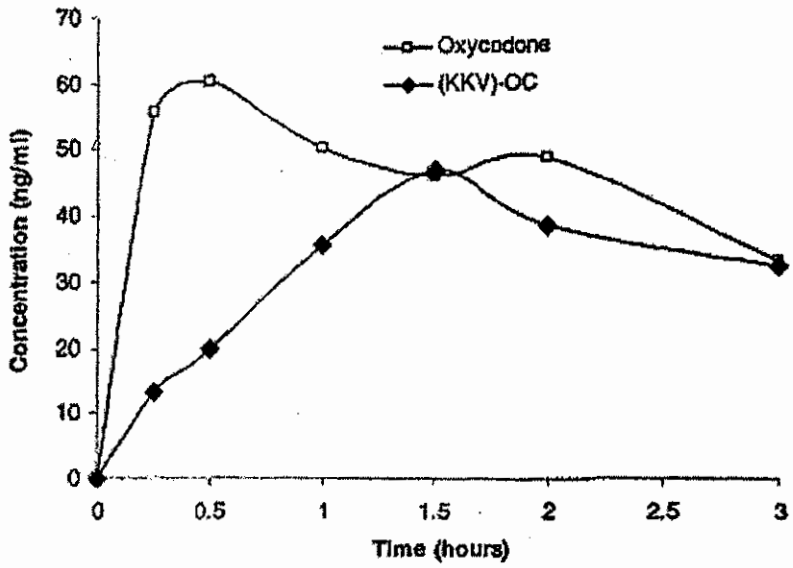

70
60
50
40
30
20
10
0
Concentration (ng/ml)
0
0.5
1
1.5
2
2.5
3
Time (hours)
Oxycodone
(KKV)-OC

Figure 159

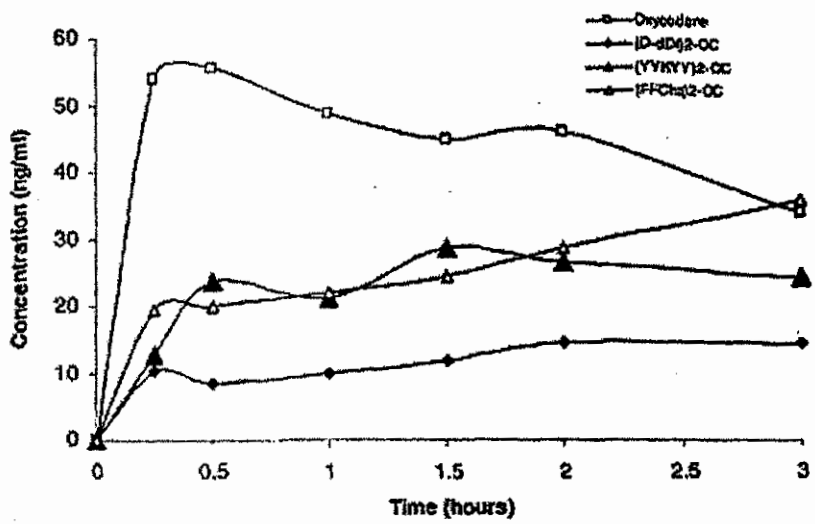

Oxycodone
(D-dDi)2-OC
(YYKYY)2-OC
(FFChs)2-OC
Concentration (ng/ml)
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
Time (hours)

Figure 160

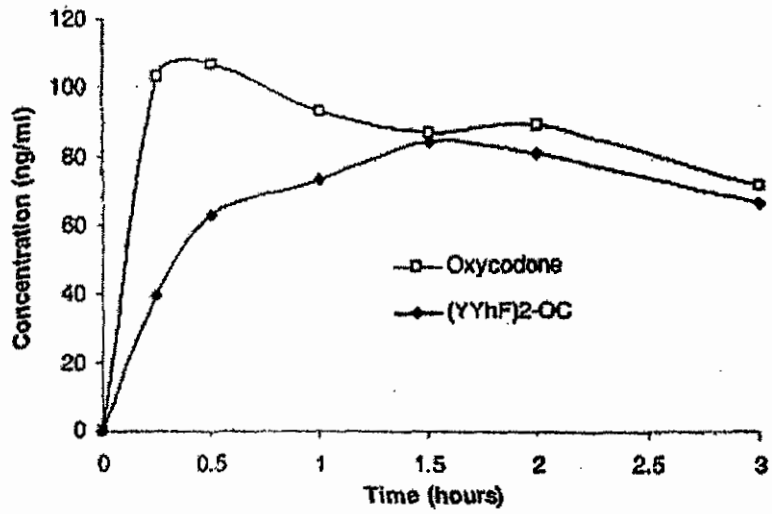

120
100
80
60
40
20
0
Concentration (ng/ml)
0
0.5
1
1.5
2
2.5
3
Time (hours)
Oxycodone
(YYhF)2-OC

Figure 161

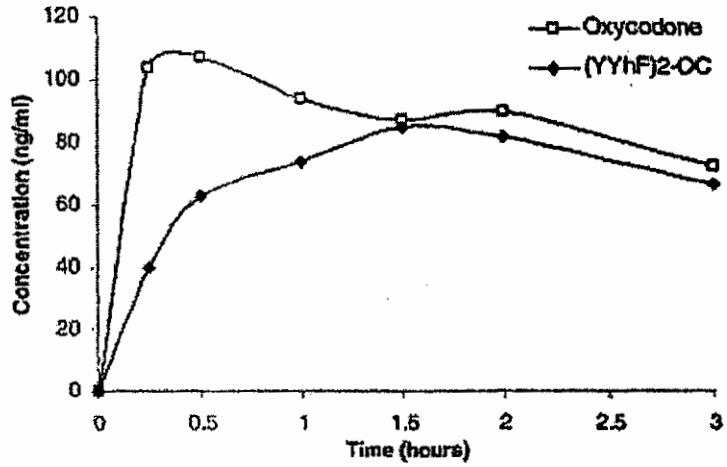

120
100
80
60
40
20
0
Concentration (ng/ml)
0
0.5
1
1.5
2
2.5
3
Time (hours)
Oxycodone
(YYhF)2-OC

Figure 162

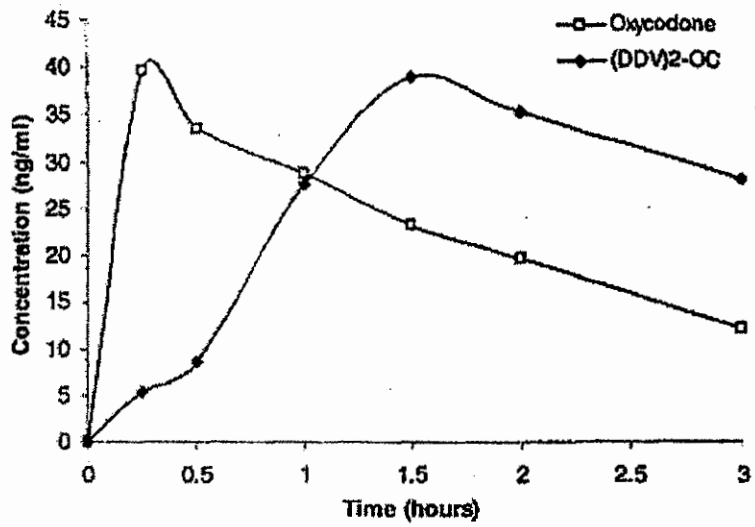

Oxycodone
(DDV)2-OC
Concentration (ng/ml)
45
40
35
30
25
20
15
10
5
0
0
0.5
1
1.5
2
2.5
3
Time (hours)

Figure 163

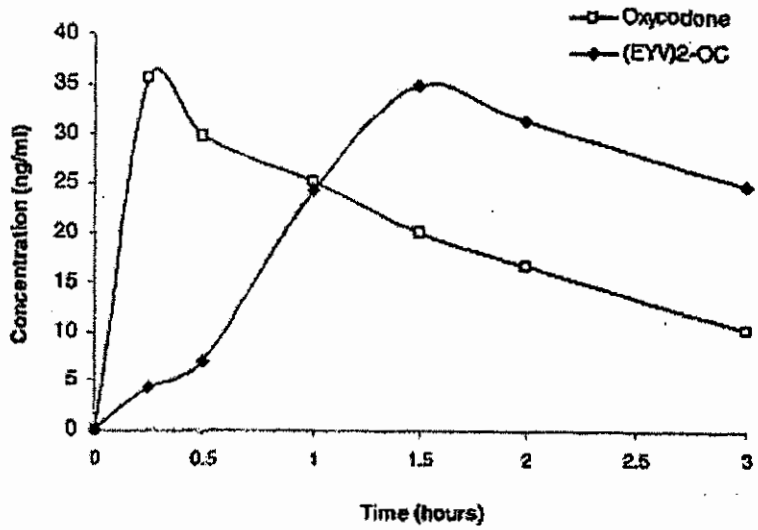

Oxycodone
(EYV)2-OC
Concentration (ng/ml)
40
35
30
25
20
15
10
5
0
0
0.5
1
1.5
2
2.5
3
Time (hours)

Figure 164

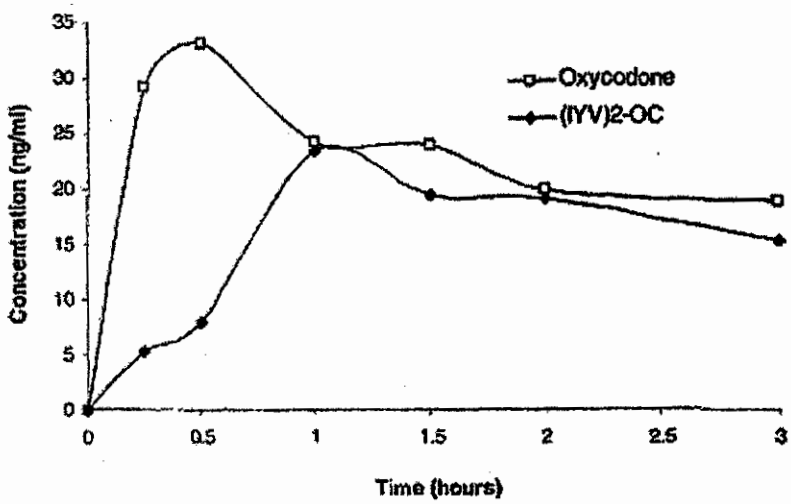

Concentration (ng/ml)
35
30
25
20
15
10
5
0
0
0.5
1
1.5
2
2.5
3
Time (hours)
Oxycodone
(IYV)2-OC

Figure 165

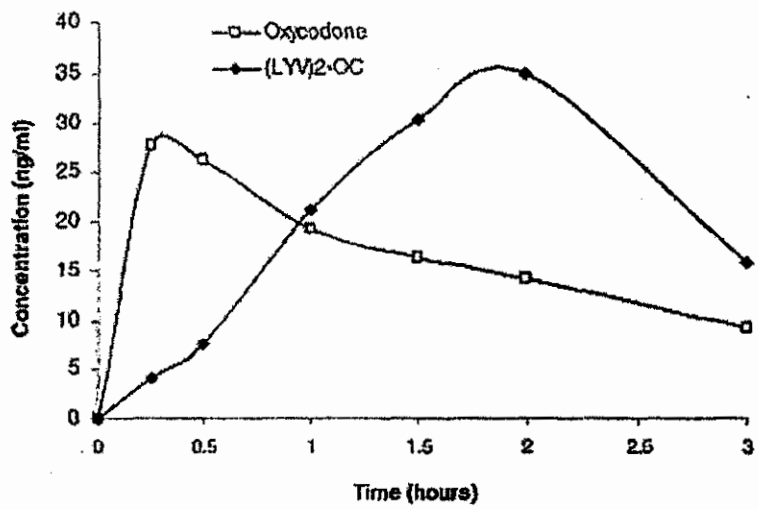

Oxycodone
(LYV)2-OC
Concentration (ng/ml)
Time (hours)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2
2.5
3

Figure 166

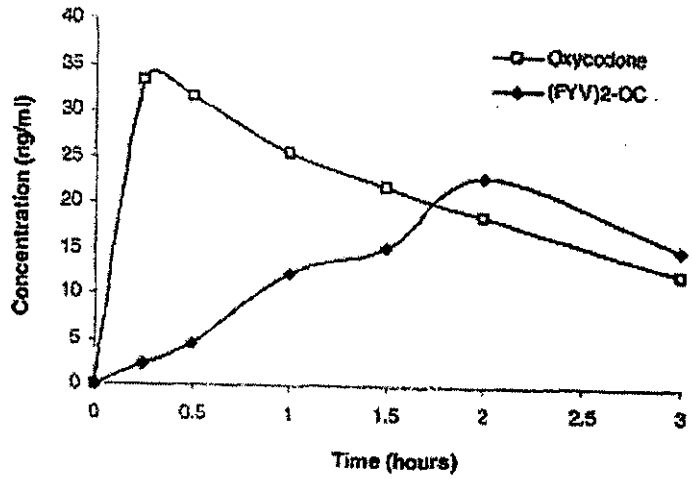

Concentration (ng/ml)
40
35
30
25
20
15
10
5
0
0
0.5
1
1.5
2
2.5
3
Time (hours)
Oxycodone
(FYV)2-OC

Figure 167

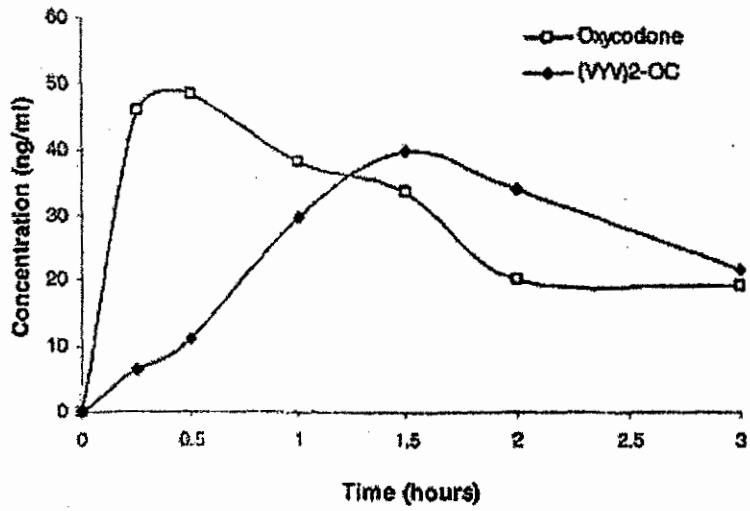

Oxycodone
(VVV)2-OC
Concentration (ng/ml)
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
Time (hours)

Figure 168

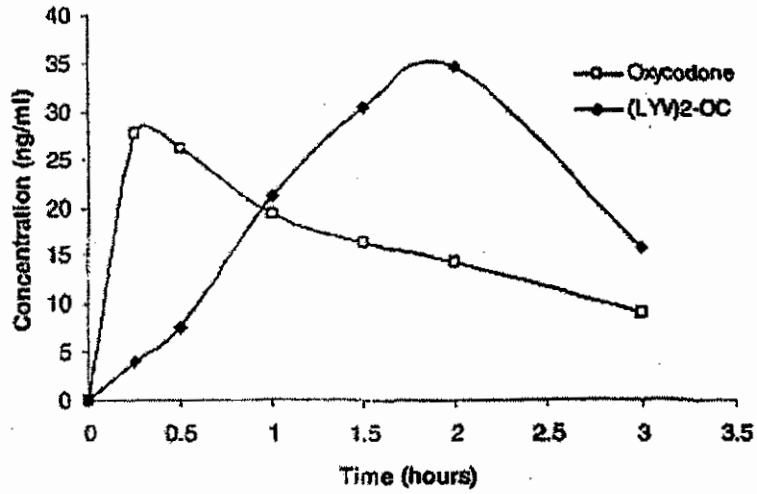

Concentration (ng/ml)
40
35
30
25
20
15
10
5
0
0
0.5
1
1.5
2
2.5
3
3.5
Time (hours)
Oxycodone
(LYV)2-OC

Figure 169

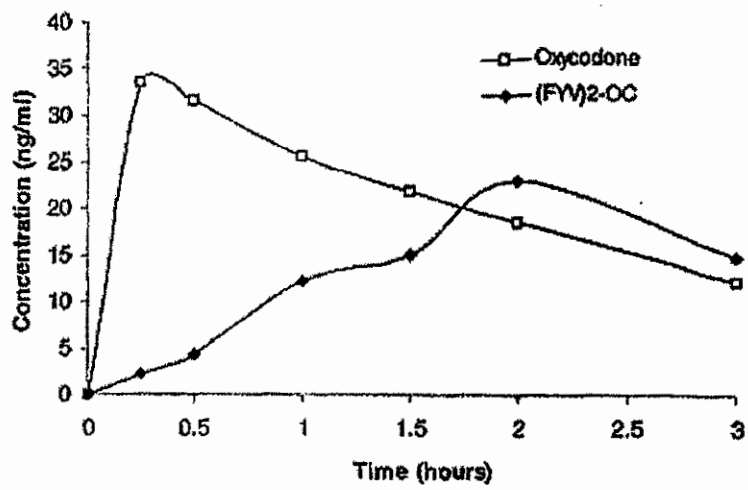

Concentration (ng/ml)
40
35
30
25
20
15
10
5
0
0
0.5
1
1.5
2
2.5
3
Time (hours)
Oxycodone
(FW)2-OC

Figure 170

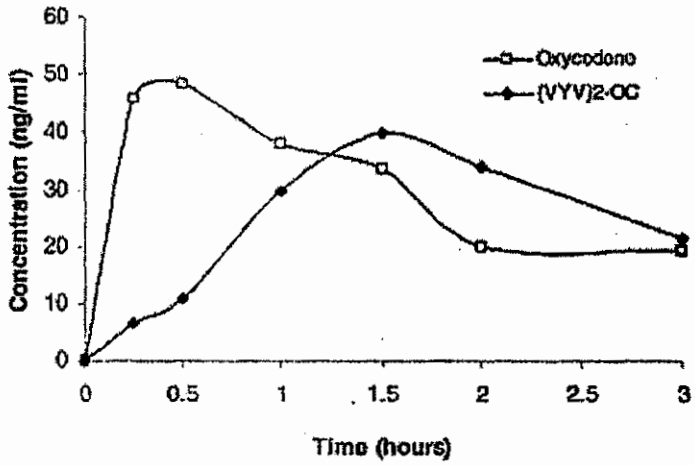

60
50
40
30
20
10
0
Concentration (ng/ml)
0
0.5
1
1.5
2
2.5
3
Time (hours)
Oxycodone
(VYV)2-OC

Figure 171

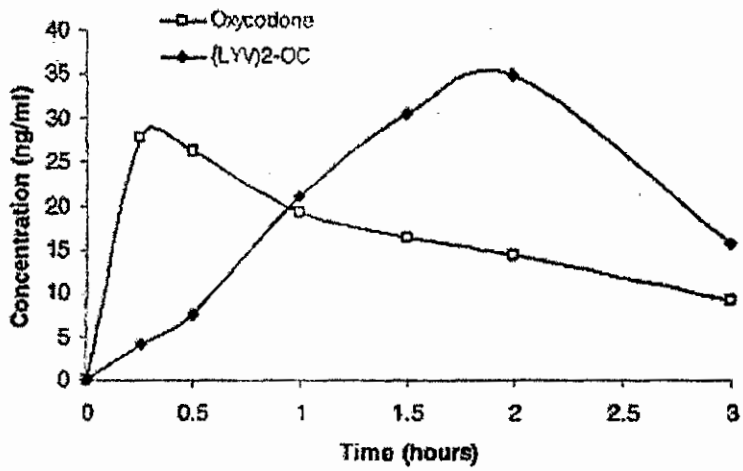

Oxycodone
(LYV)2-OC
Concentration (ng/ml)
40
35
30
25
20
15
10
5
0
0
0.5
1
1.5
2
2.5
3
Time (hours)

Figure 172

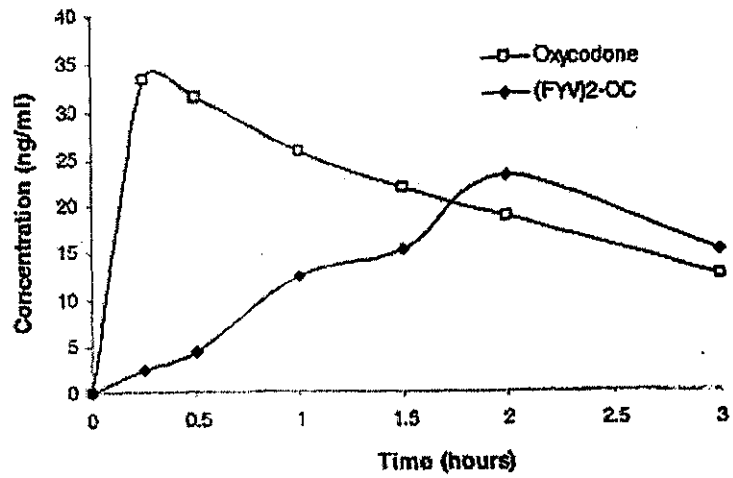

Oxycodone
(FYV)2-OC
Concentration (ng/ml)
Time (hours)
0
5
10
15
20
25
30
35
40
0
0.5
1
1.5
2
2.5
3

Figure 173

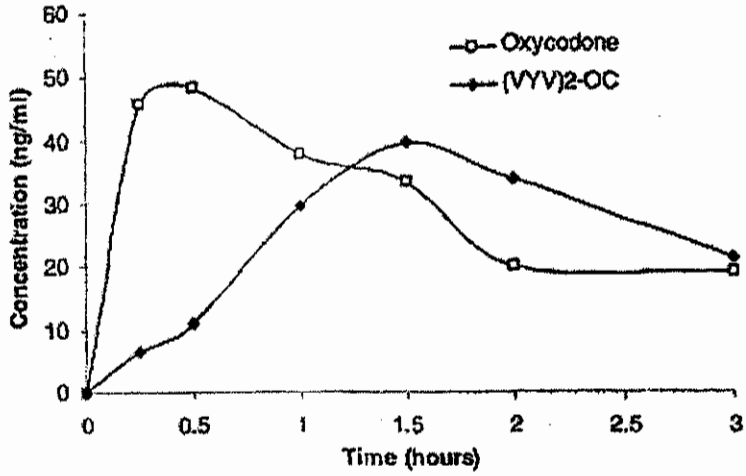

Oxycodone
(VYV)2-OC
Concentration (ng/ml)
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
Time (hours)

Figure 174

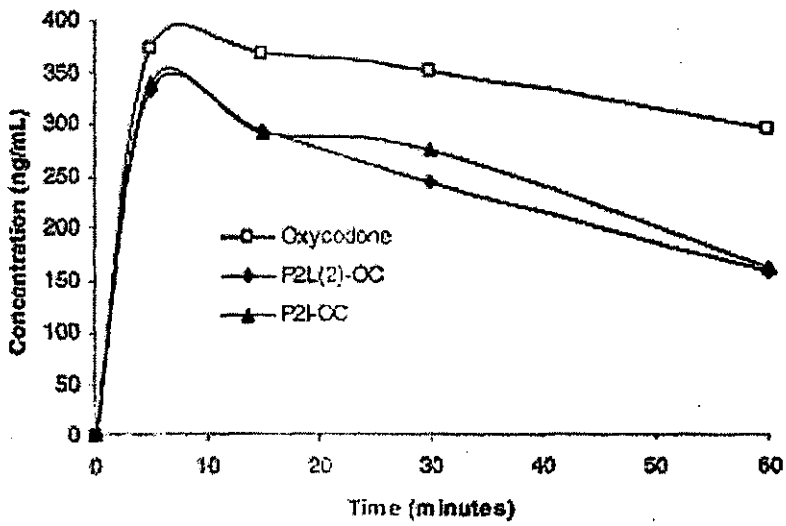

Concentration (ng/mL)
400
350
300
250
200
150
100
50
0
0
10
20
30
40
50
60
Time (minutes)
Oxycodone
P2L(2)-OC
P2I-OC

Figure 175

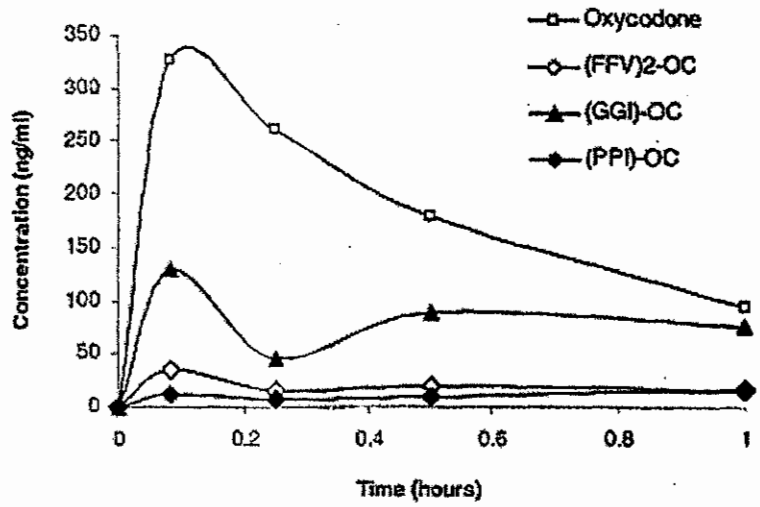

Oxycodone
(FFV)2-OC
(GGI)-OC
(PPI)-OC
Concentration (ng/ml)
350
300
250
200
150
100
50
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 176

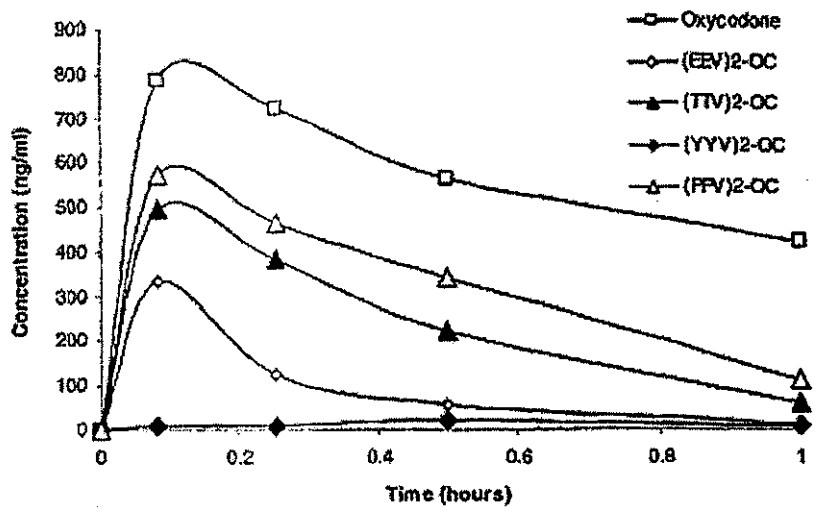

Oxycodone
(EEV)2-OC
(TTV)2-OC
(YYV)2-OC
(FFV)2-OC
Concentration (ng/ml)
900
800
700
600
500
400
300
200
100
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 177

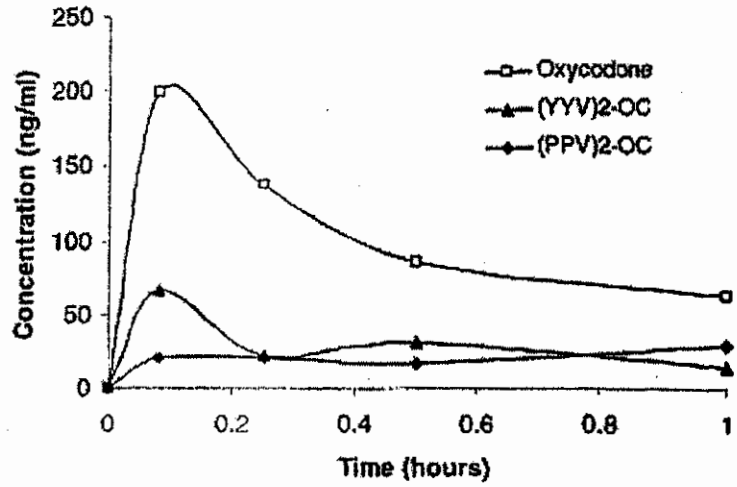

250
200
150
100
50
0
Concentration (ng/ml)
0
0.2
0.4
0.6
0.8
1
Time (hours)
Oxycodone
(YYV)2-OC
(PPV)2-OC

Figure 178

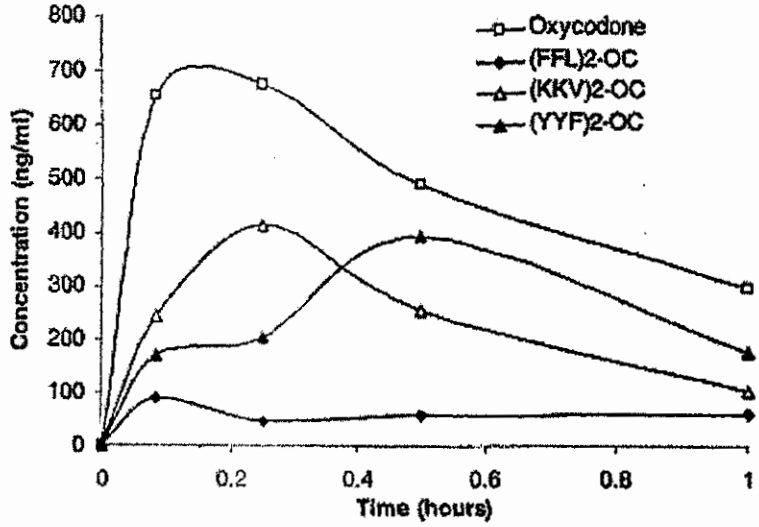

Oxycodone
(FFL)2-OC
(KKV)2-OC
(YYF)2-OC
Concentration (ng/ml)
800
700
600
500
400
300
200
100
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 179

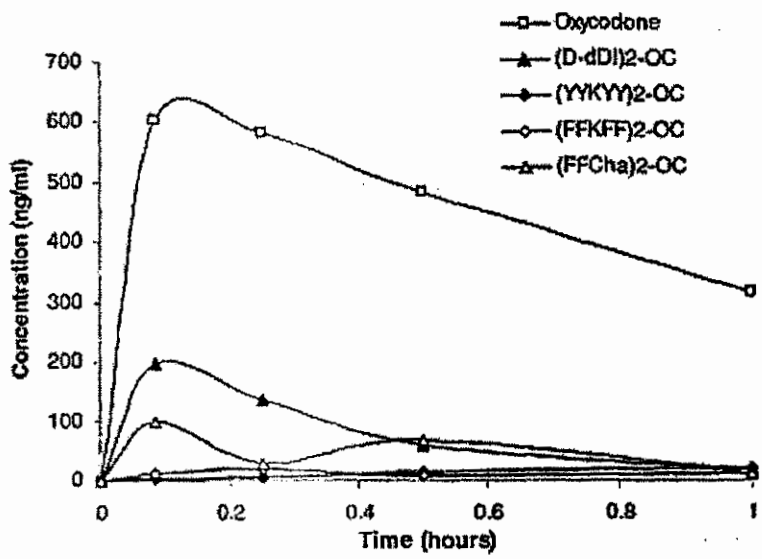

Oxycodone
(D-dDI)2-OC
(YYKYY)2-OC
(FFKFF)2-OC
(FFCha)2-OC
Concentration (ng/ml)
700
600
500
400
300
200
100
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 180

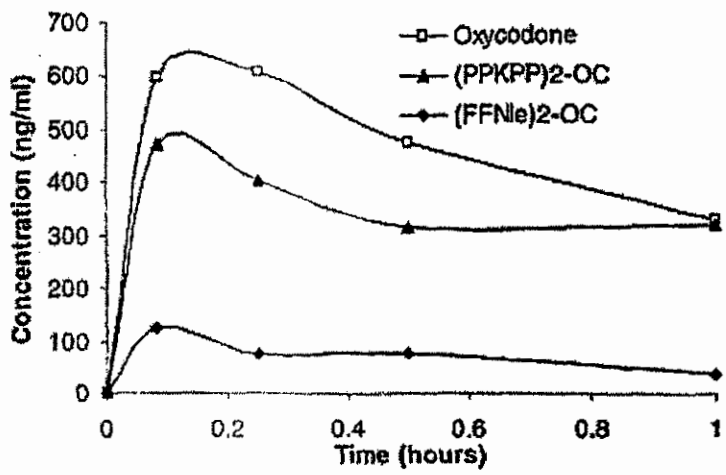

700
600
500
400
300
200
100
0
Concentration (ng/ml)
0
0.2
0.4
0.6
0.8
1
Time (hours)
Oxycodone
(PPKPP)2-OC
(FFNle)2-OC

Figure 181

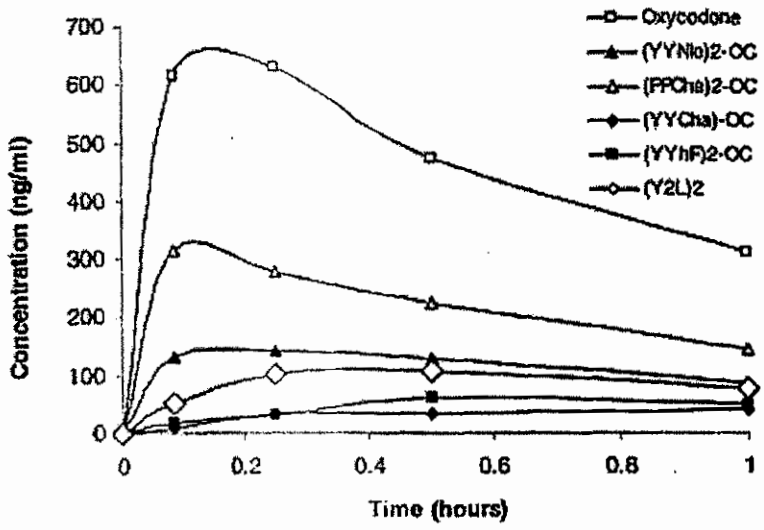

Oxycodone
(YYNle)2-OC
(PPCha)2-OC
(YYCha)-OC
(YYhF)2-OC
(Y2L)2
Concentration (ng/ml)
700
600
500
400
300
200
100
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 182

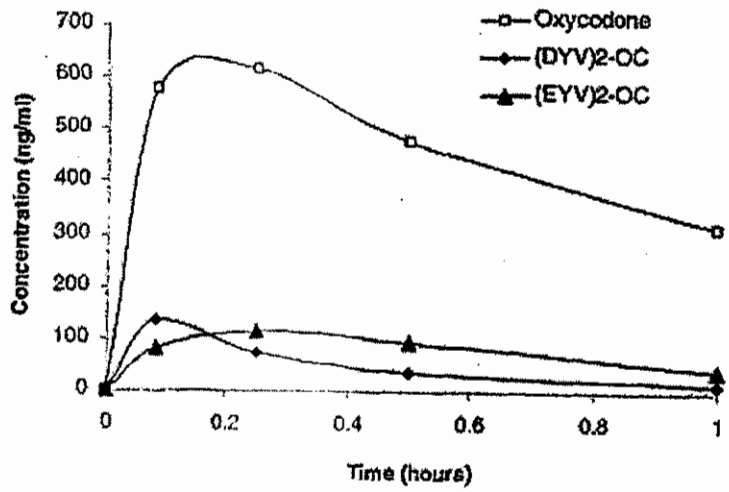

Oxycodone
(DYV)2-OC
(EYV)2-OC
Concentration (ng/ml)
700
600
500
400
300
200
100
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 183

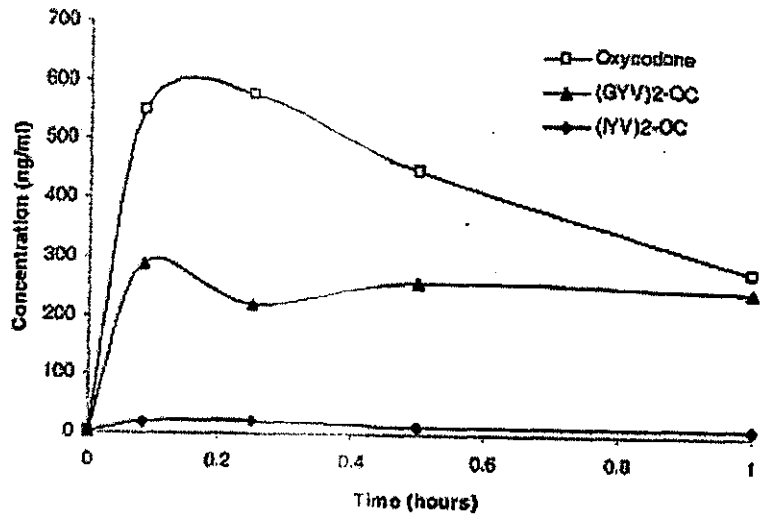

700
600
500
400
300
200
100
0
Concentration (ng/ml)
0
0.2
0.4
0.6
0.8
1
Time (hours)
Oxycodone
(GYV)2-OC
(YV)2-OC

Figure 184

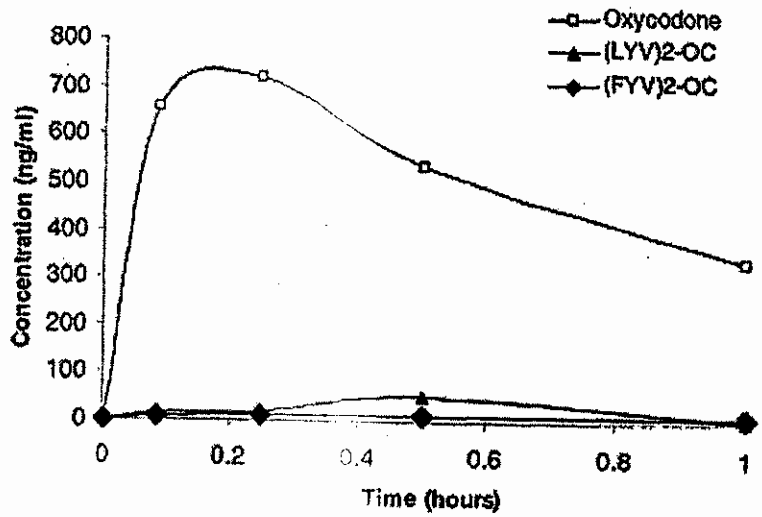

Oxycodone
(LYV)2-OC
(FYV)2-OC
Concentration (ng/ml)
800
700
600
500
400
300
200
100
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 185

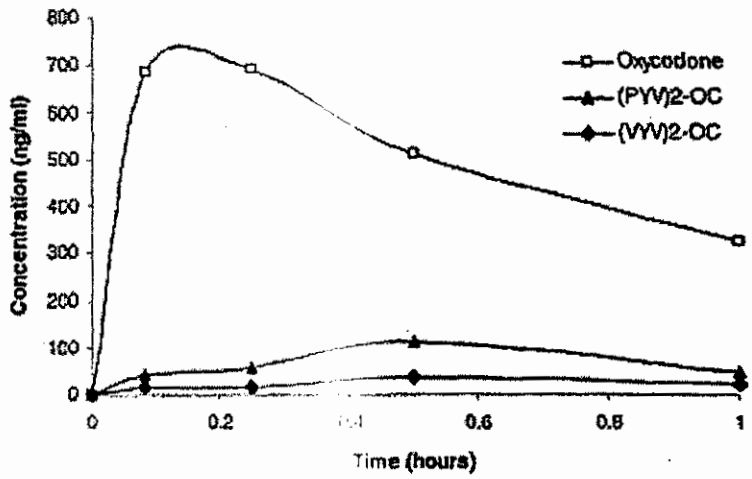

800
700
600
500
400
300
200
100
0
Concentration (ng/ml)
0
0.2
0.6
0.8
1
Time (hours)
Oxycodone
(PYY)2-OC
(YYY)2-OC

Figure 186

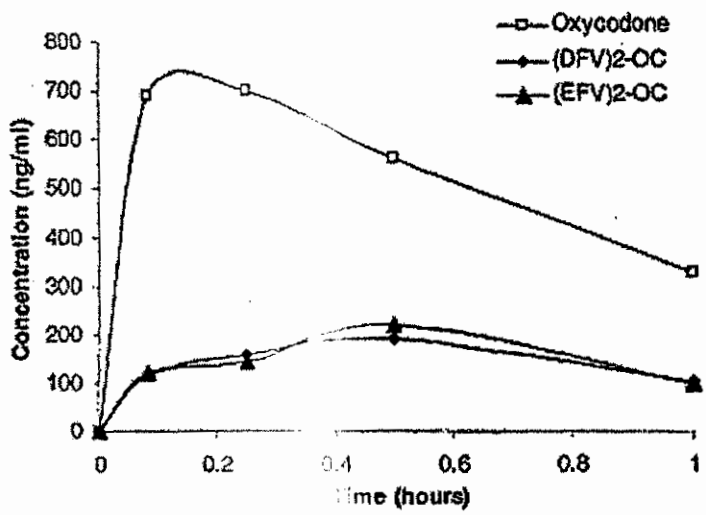

Oxycodone
(DFV)2-OC
(EFV)2-OC
Concentration (ng/ml)
800
700
600
500
400
300
200
100
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 187

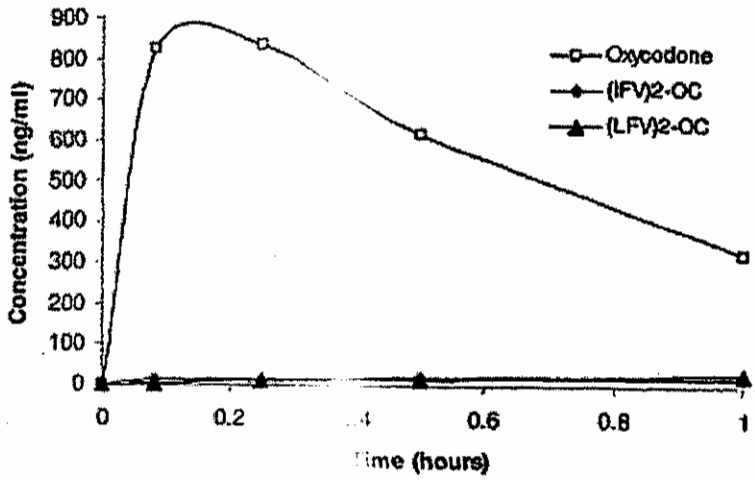

900
800
700
600
500
400
300
200
100
0
Concentration (ng/ml)
0
0.2
0.6
0.8
1
Time (hours)
Oxycodone
(IFV)2-OC
(LFV)2-OC

Figure 188

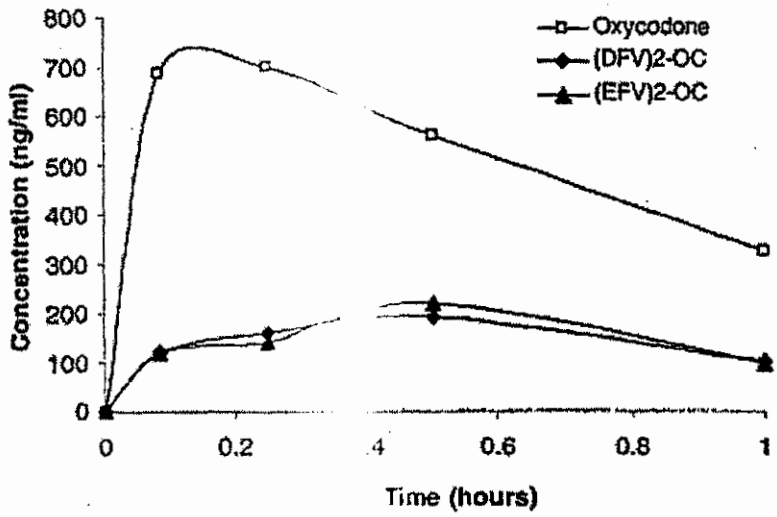

Oxycodone
(DFV)2-OC
(EFV)2-OC
Concentration (ng/ml)
800
700
600
500
400
300
200
100
0
0
0.2
0.6
0.8
1
Time (hours)

Figure 189

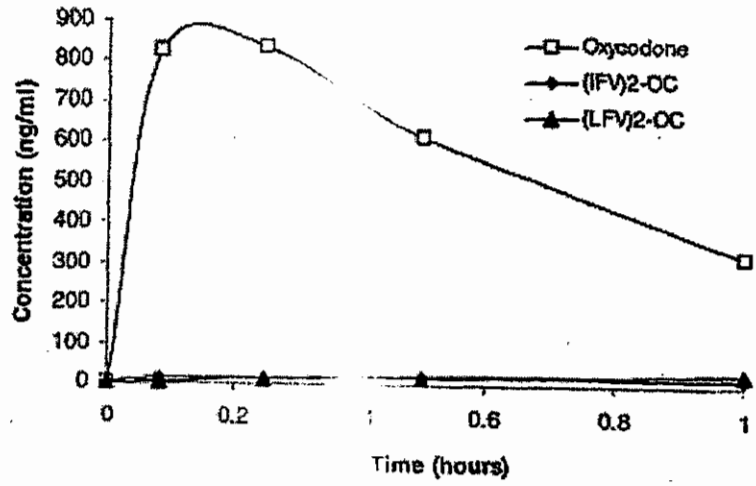

900
800
700
600
500
400
300
200
100
0
Concentration (ng/ml)
0
0.2
0.6
0.8
1
Time (hours)
Oxycodone
(IFV)2-OC
(LFV)2-OC

Figure 190

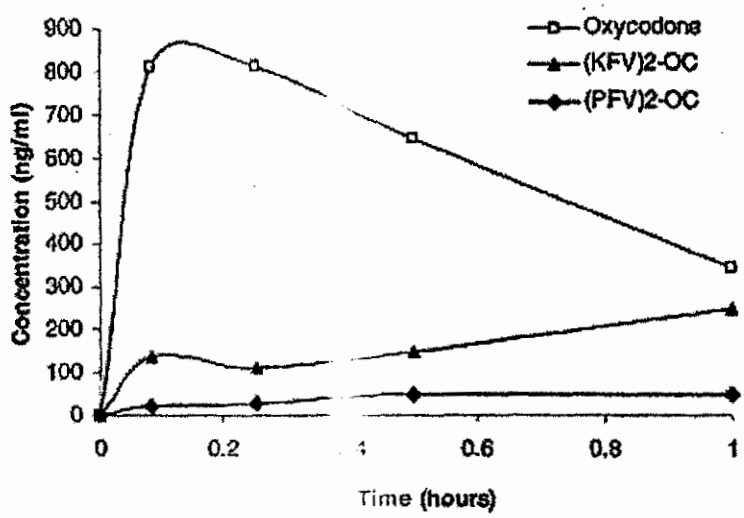

Oxycodone
(KFV)2-OC
(PFV)2-OC
Concentration (ng/ml)
900
800
700
600
500
400
300
200
100
0
0
0.2
0.6
0.8
1
Time (hours)

Figure 191

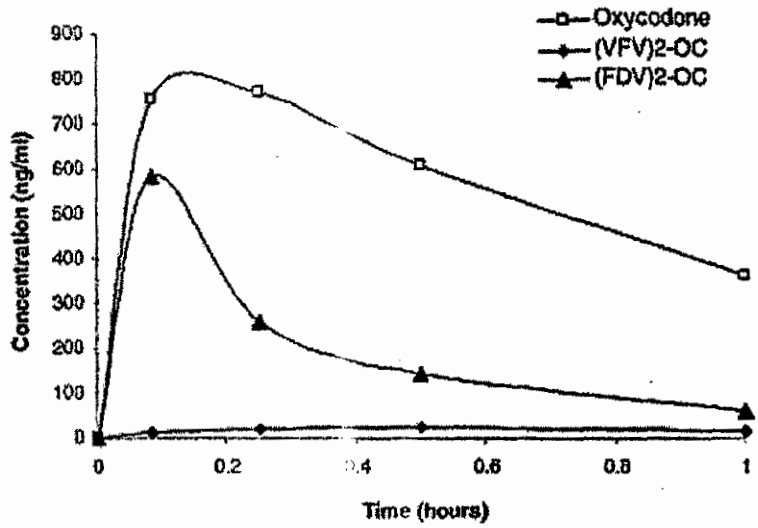

Oxycodone
(VFV)2-OC
(FDV)2-OC
Concentration (ng/ml)
900
800
700
600
500
400
300
200
100
0
0
0.2
0.4
0.6
0.8
1
Time (hours)

Figure 192

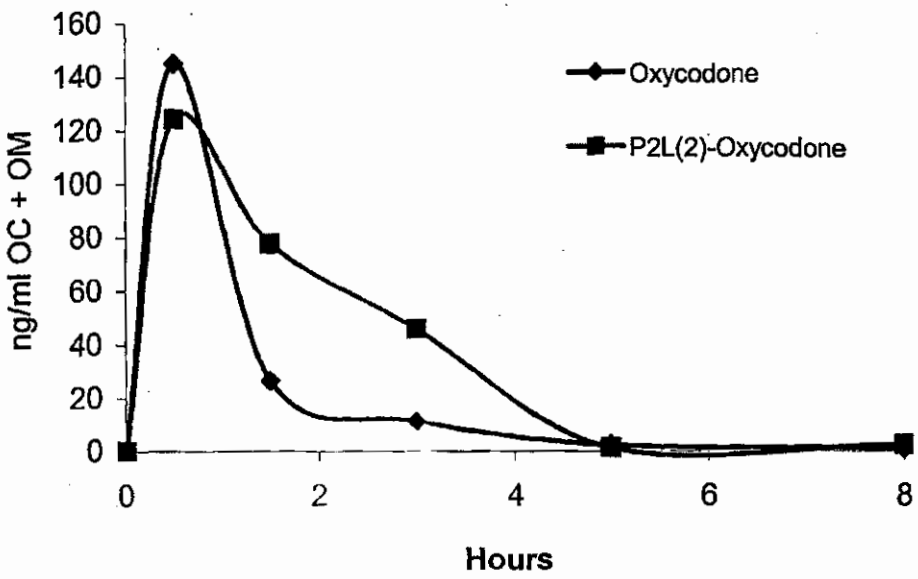

160
140
120
100
80
60
40
20
0
ng/ml OC + OM
0
2
4
6
8
Hours
Oxycodone
P2L(2)-Oxycodone

Figure 193

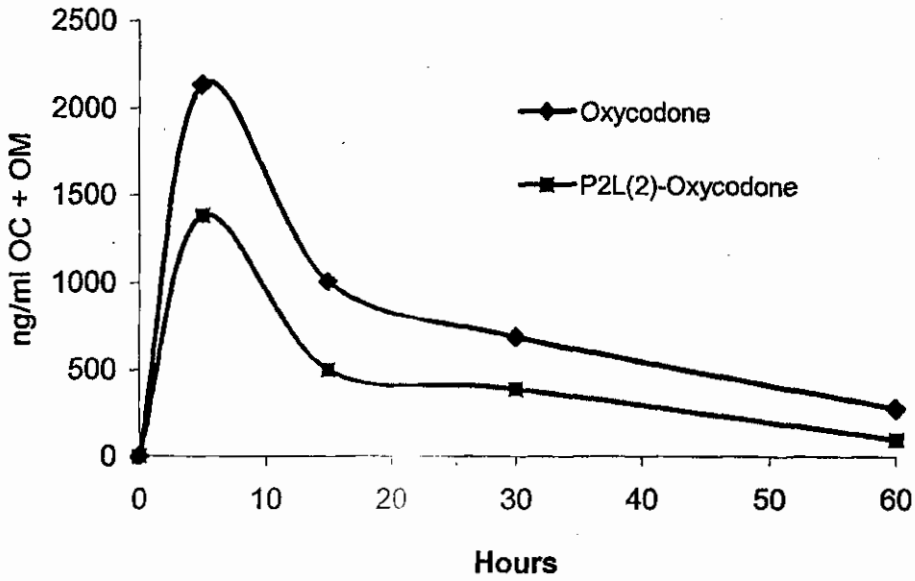

2500
2000
1500
1000
500
0
ng/ml OC + OM
0
10
20
30
40
50
60
Hours
Oxycodone
P2L(2)-Oxycodone

Figure 194

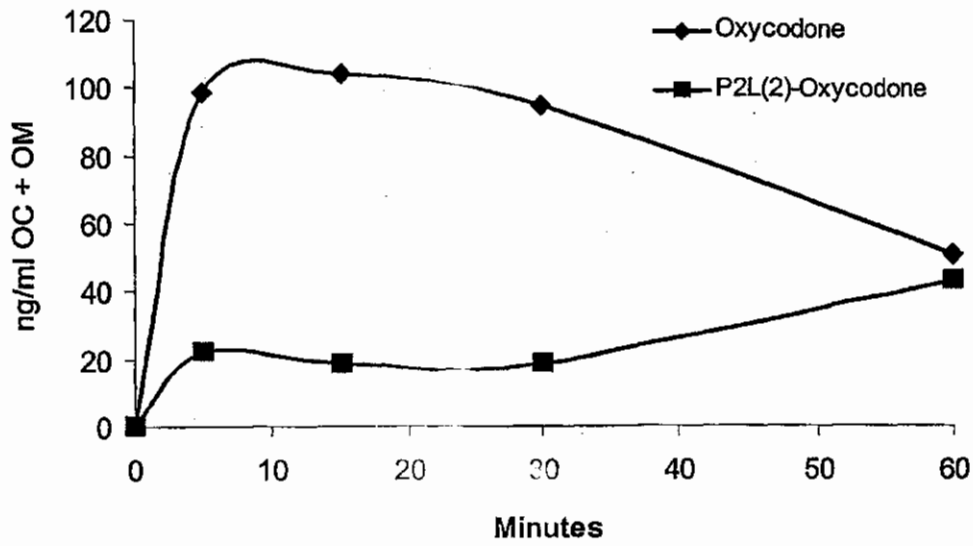

120
100
80
60
40
20
0
ng/ml OC + OM
0
10
20
30
40
50
60
Minutes
Oxycodone
P2L(2)-Oxycodone

Figure 195