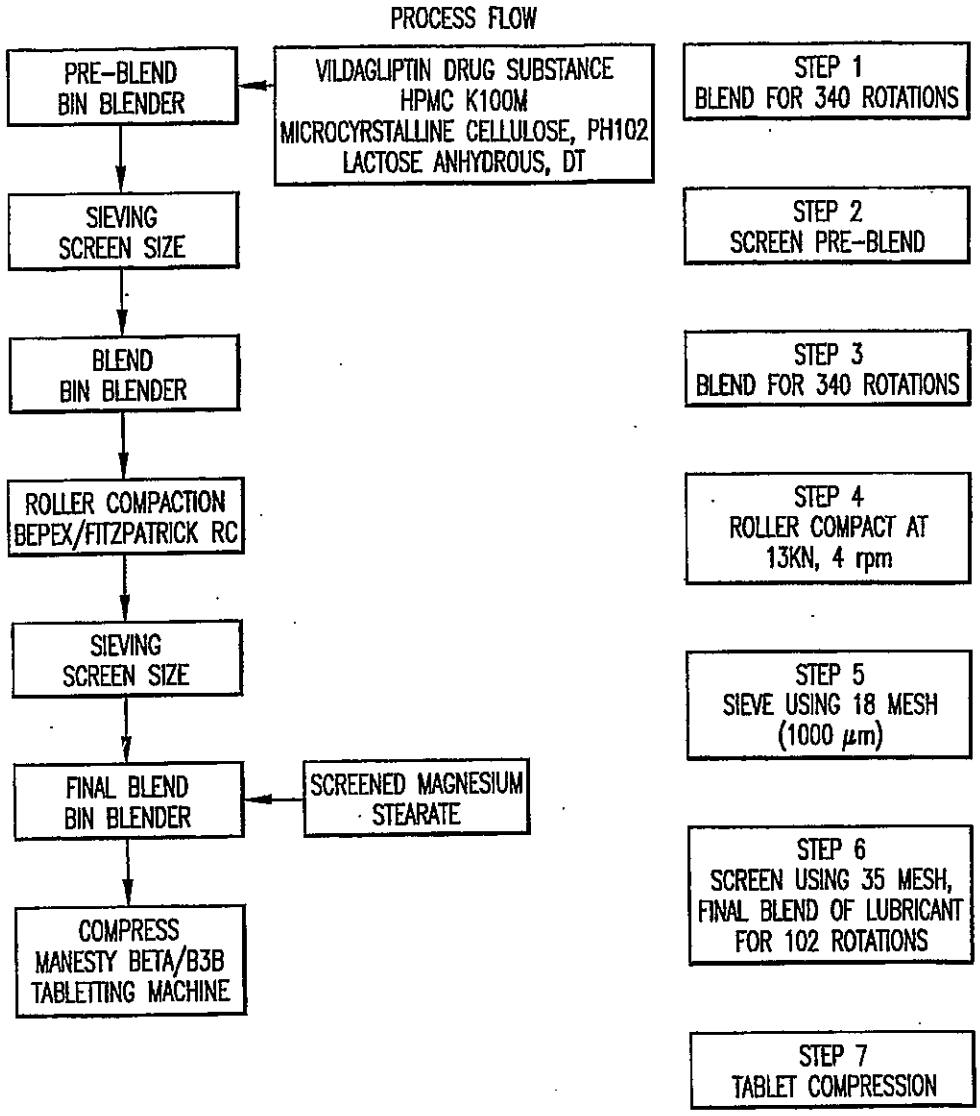

PROCESS FLOW
PRE-BLEND BIN BLENDER
VILDAGLIPTIN DRUG SUBSTANCE
HPMC K100M
MICROCYRSTALLINE CELLULOSE, PH102
LACTOSE ANHYDROUS, DT
STEP 1
BLEND FOR 340 ROTATIONS
SIEVING SCREEN SIZE
STEP 2
SCREEN PRE-BLEND
BLEND BIN BLENDER
STEP 3
BLEND FOR 340 ROTATIONS
ROLLER COMPACTION BEPEX/FITZPATRICK RC
STEP 4
ROLLER COMPACT AT 13KN, 4 rpm
SIEVING SCREEN SIZE
STEP 5
SIEVE USING 18 MESH (1000 μm)
FINAL BLEND BIN BLENDER
SCREENED MAGNESIUM STEARATE
STEP 6
SCREEN USING 35 MESH, FINAL BLEND OF LUBRICANT FOR 102 ROTATIONS
COMPRESS MANESTY BETA/B3B TABLETTING MACHINE
STEP 7
TABLET COMPRESSION

FIG. 1

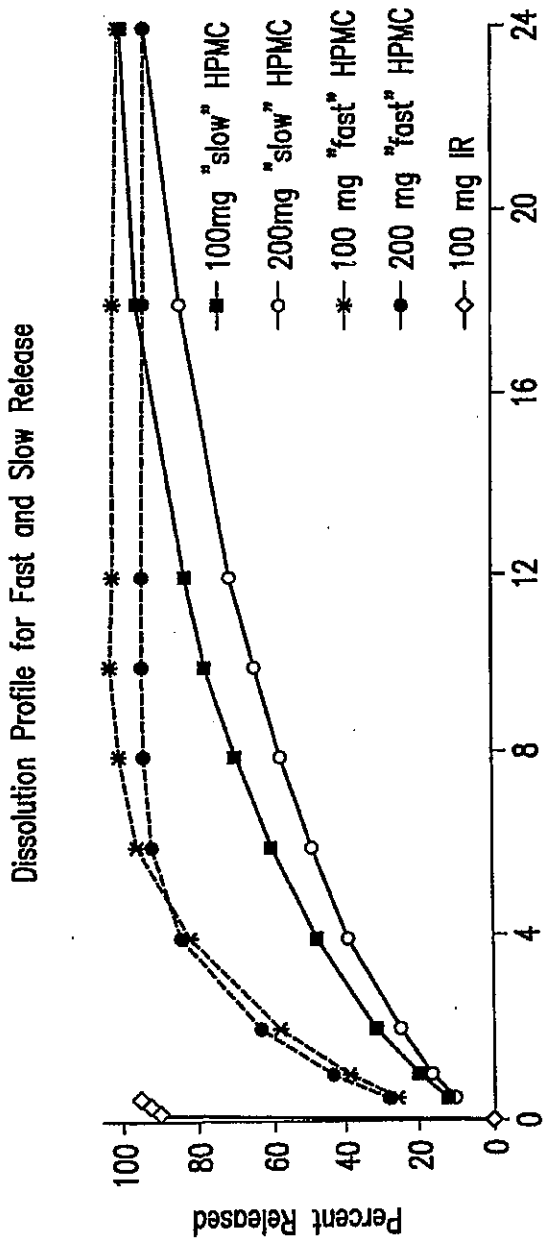

Dissolution Profile for Fast and Slow Release
Percent Released
Hours
100
80
60
40
20
0
0
4
8
12
16
20
24
100mg "slow" HPMC
200mg "slow" HPMC
100 mg "fast" HPMC
200 mg "fast" HPMC
100 mg IR

FIG.2

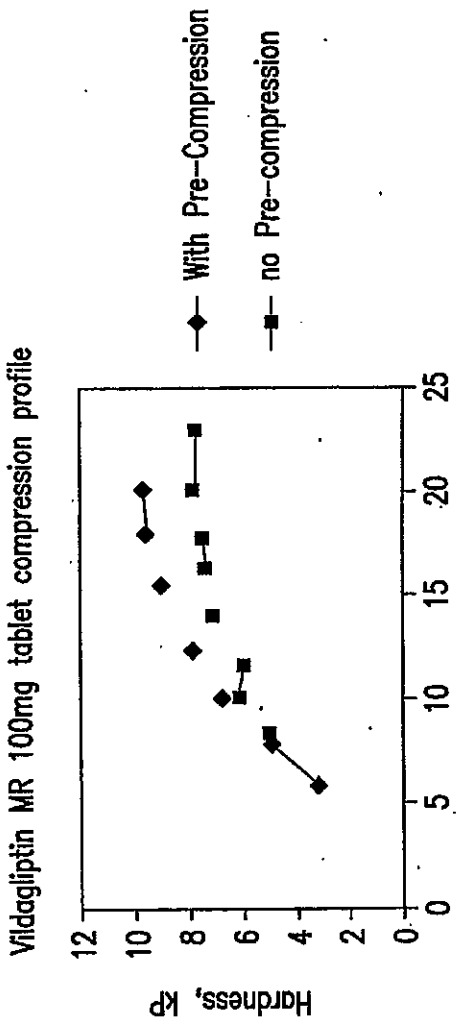

Vildagliptin MR 100mg tablet compression profile
With Pre-Compression
no Pre-compression
Hardness, kP
0
2
4
6
8
10
12
0
5
10
15
20
25
Comp F, kN

FIG.3

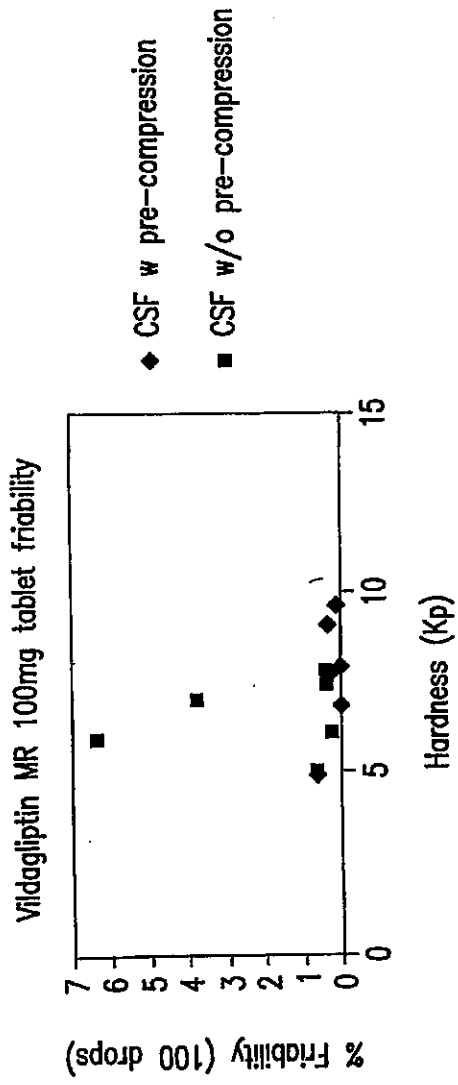

Vildagliptin MR 100mg tablet friability
◆ CSF w pre-compression
■ CSF w/o pre-compression
% Friability (100 drops)
Hardness (Kp)
0
1
2
3
4
5
6
7
0
5
10
15

FIG.4

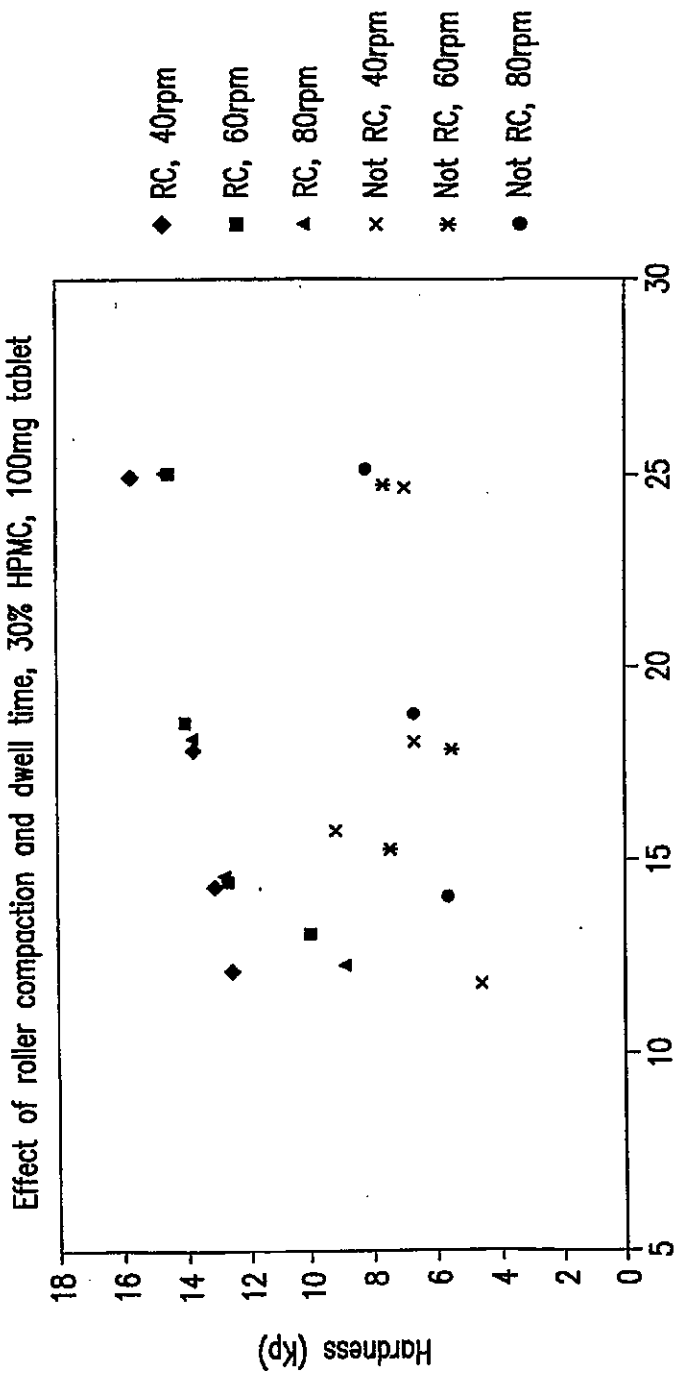

Effect of roller compaction and dwell time, 30% HPMC, 100mg tablet
RC, 40rpm
RC, 60rpm
RC, 80rpm
Not RC, 40rpm
Not RC, 60rpm
Not RC, 80rpm
Hardness (kp)
Comp F, (kN)
0
2
4
6
8
10
12
14
16
18
5
10
15
20
25
30

FIG.5

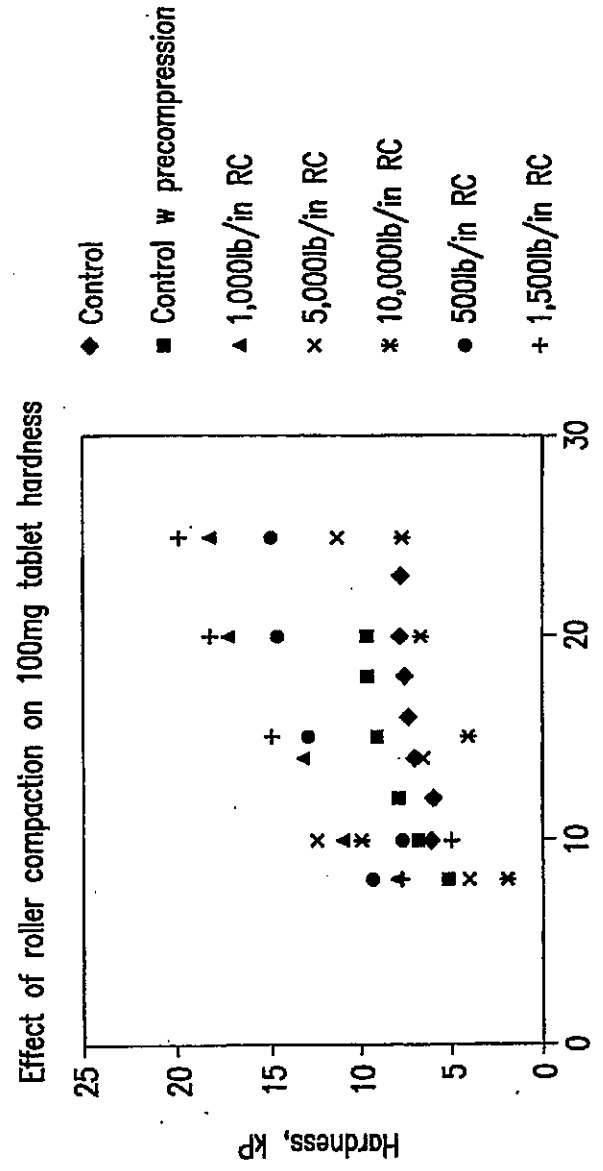

Effect of roller compaction on 100mg tablet hardness
◆ Control
■ Control w precompression
▲ 1,000lb/in RC
× 5,000lb/in RC
* 10,000lb/in RC
● 500lb/in RC
+ 1,500lb/in RC
Hardness, kP
0
5
10
15
20
25
0
10
20
30
Comp F, kN

FIG.6

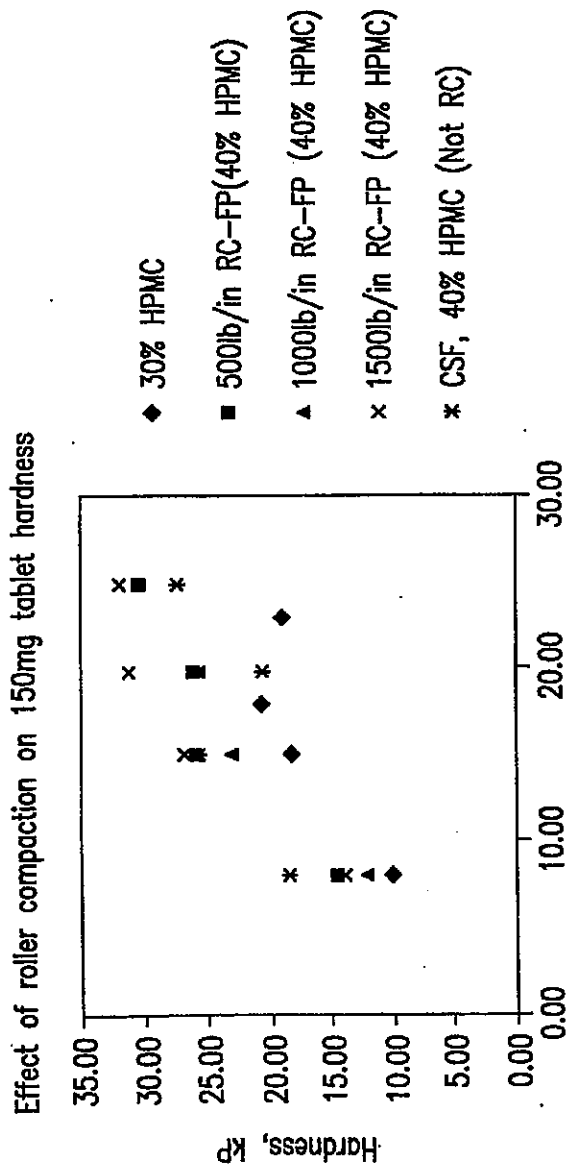

Effect of roller compaction on 150mg tablet hardness
Hardness, kP
35.00
30.00
25.00
20.00
15.00
10.00
5.00
0.00
0.00
10.00
20.00
30.00
Comp F, kN
◆ 30% HPMC
■ 500lb/in RC-FP(40% HPMC)
▲ 1000lb/in RC-FP (40% HPMC)
× 1500lb/in RC-FP (40% HPMC)
✱ CSF, 40% HPMC (Not RC)

FIG. 7

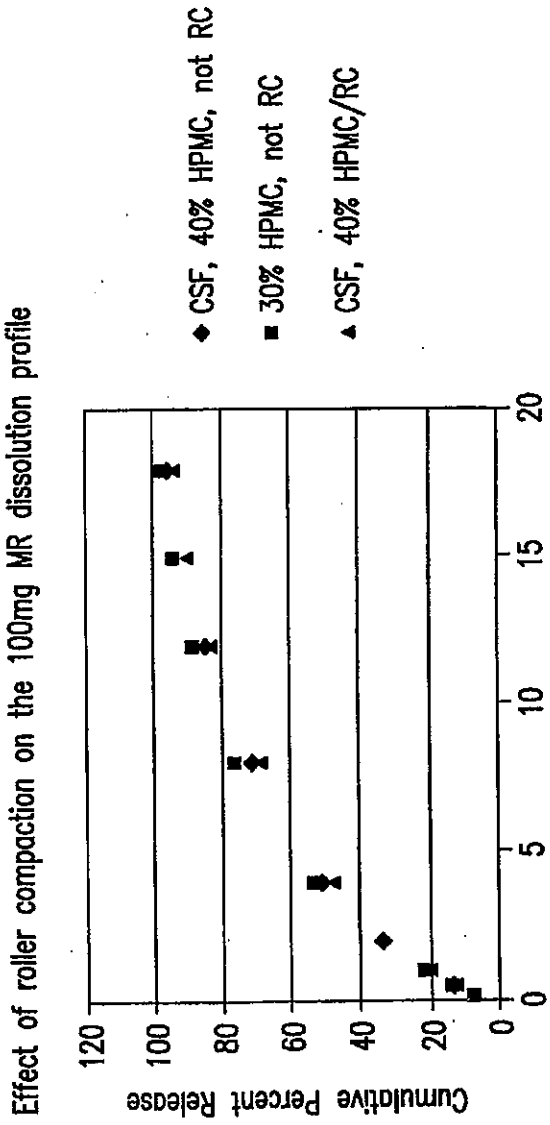

Effect of roller compaction on the 100mg MR dissolution profile
◆ CSF, 40% HPMC, not RC
■ 30% HPMC, not RC
▲ CSF, 40% HPMC/RC
Cumulative Percent Release
120
100
80
60
40
20
0
0
5
10
15
20
Time (Hrs)

FIG.8

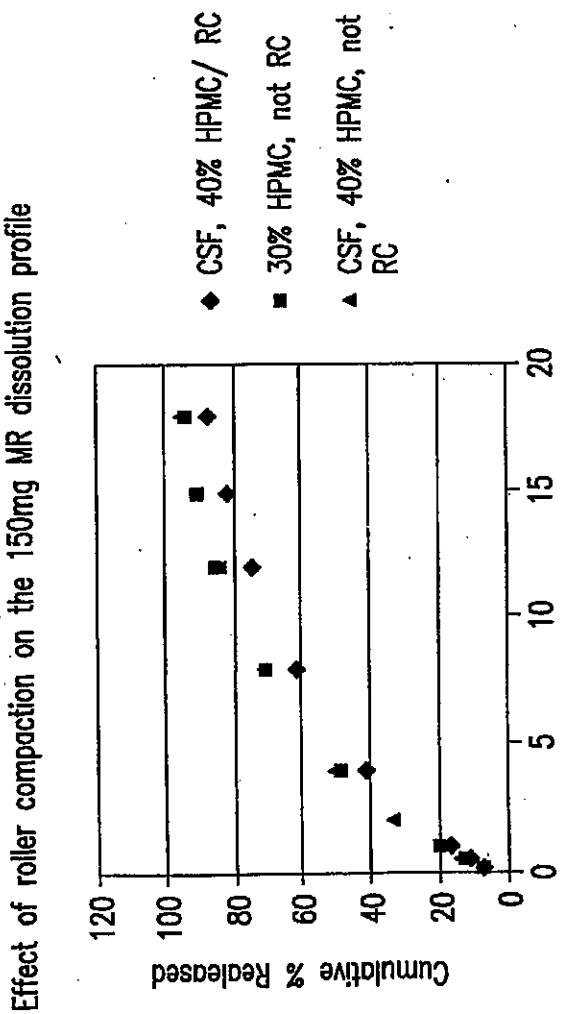

Effect of roller compaction on the 150mg MR dissolution profile
CSF, 40% HPMC/ RC
30% HPMC, not RC
CSF, 40% HPMC, not RC
Cumulative % Redleased
120
100
80
60
40
20
0
0
5
10
15
20
Times (hrs)

FIG.9

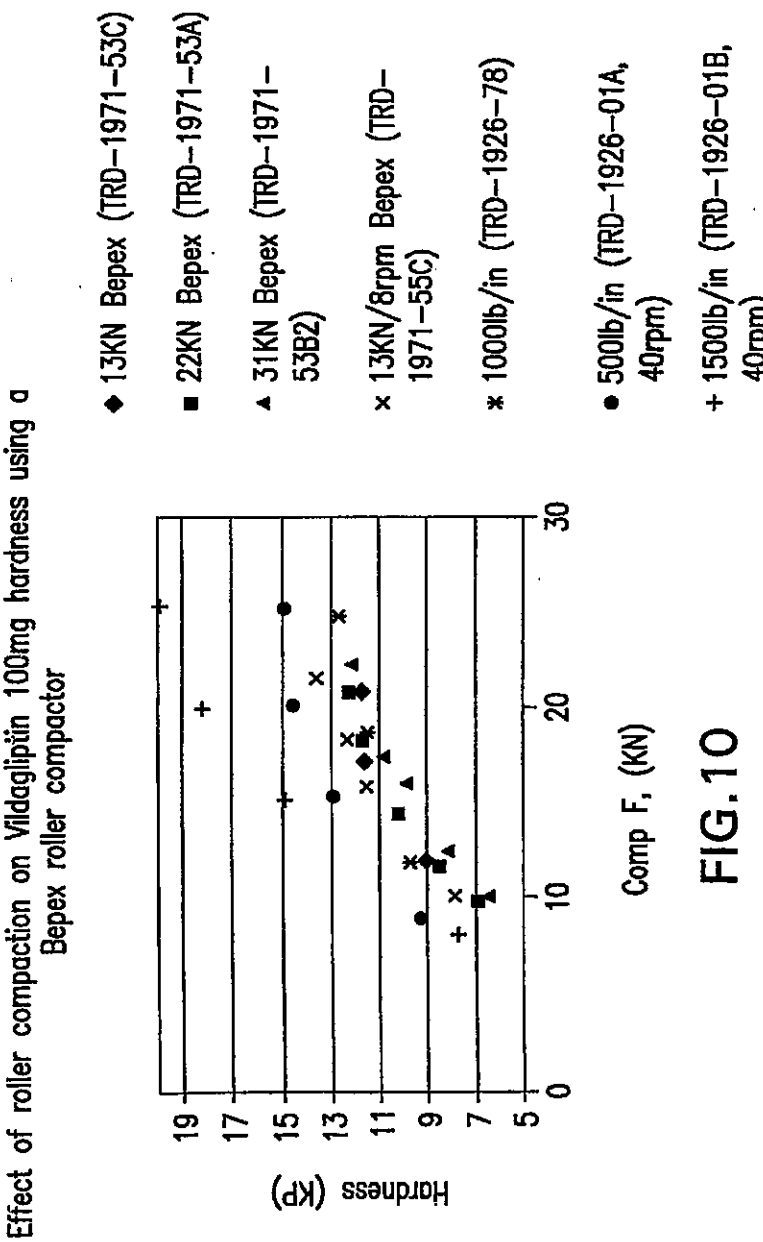

Effect of roller compaction on Vildagliptin 100mg hardness using a Bepex roller compactor
◆ 13KN Bepex (TRD-1971-53C)
■ 22KN Bepex (TRD-1971-53A)
▲ 31KN Bepex (TRD-1971-53B2)
× 13KN/8rpm Bepex (TRD-1971-55C)
* 1000lb/in (TRD-1926-78)
● 500lb/in (TRD-1926-01A, 40rpm)
+ 1500lb/in (TRD-1926-01B, 40rpm)
Hardness (KP)
19
17
15
13
11
9
7
5
0
10
20
30
Comp F, (KN)

FIG. 10

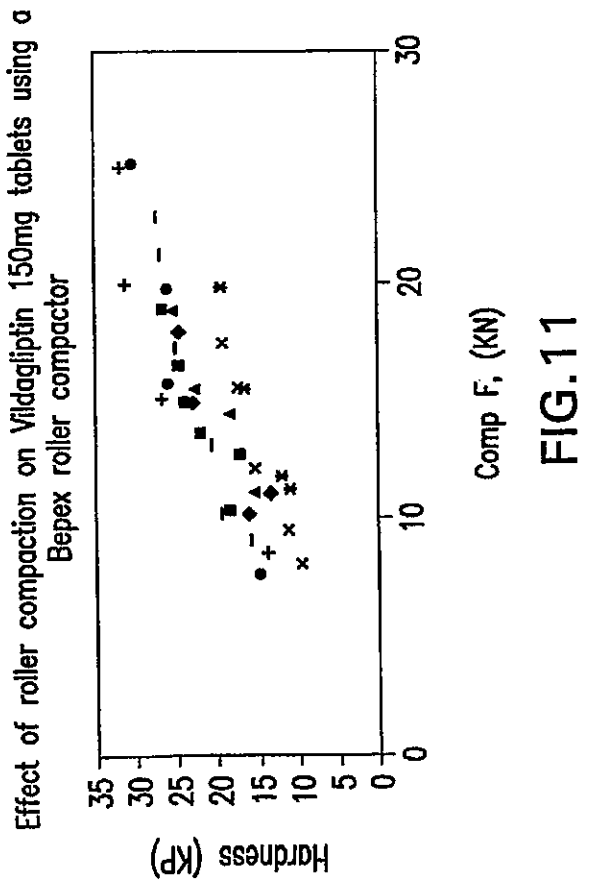

Effect of roller compaction on Vildagliptin 150mg tablets using a Bepex roller compactor
Hardness (KP)
Comp F, (KN)
0
5
10
15
20
25
30
35
0
10
20
30
◆ 13KN/4rpm (TRD-1971-55A)
■ 13KN/6rpm Bepex (TRD-1971-55B)
▲ 13KN/8rpm Bepex (TRD-1971-55C)
× 22KN/4rpm Bepex (TRD-1971-53A)
* 31KN/4rpm Bepex (TRD-1971-53B2)
● 500lb/in (TRD-1926-01A)
+ 1500lb/in (TRD-1926-01B)
- 1000lb/in (TRD-1926-78)

FIG. 11

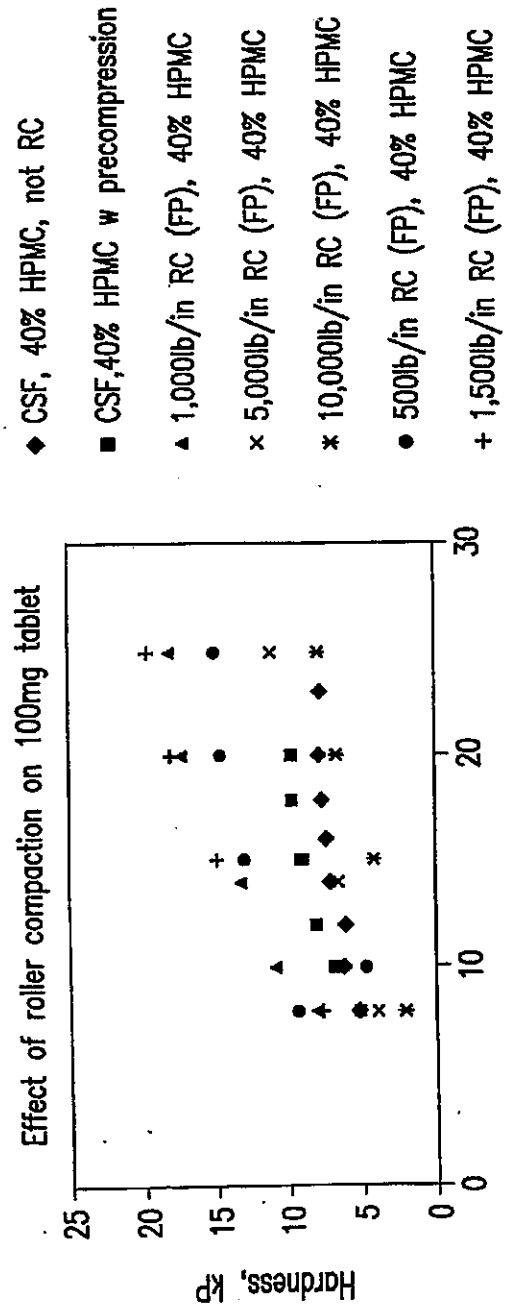

Effect of roller compaction on 100mg tablet
Hardness, kP
Comp F, kN
◆ CSF, 40% HPMC, not RC
■ CSF,40% HPMC w precompression
▲ 1,000lb/in RC (FP), 40% HPMC
× 5,000lb/in RC (FP), 40% HPMC
* 10,000lb/in RC (FP), 40% HPMC
● 500lb/in RC (FP), 40% HPMC
+ 1,500lb/in RC (FP), 40% HPMC

FIG.12

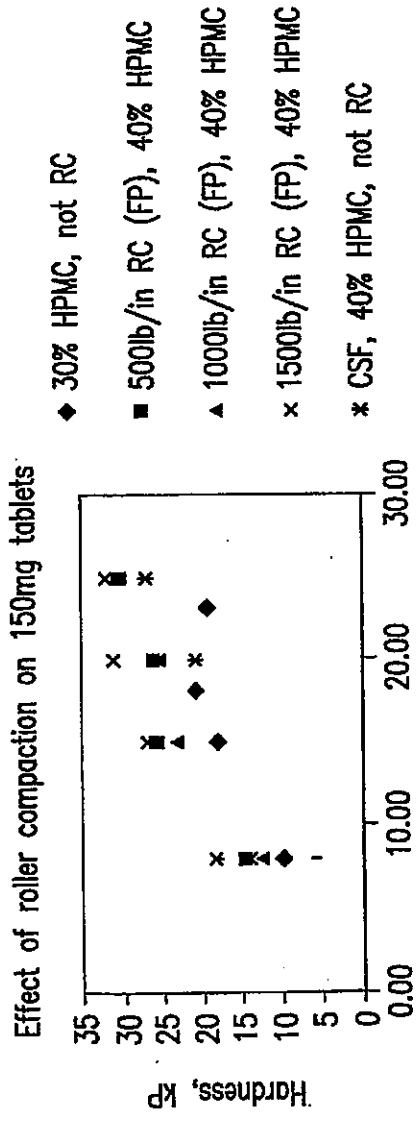

Effect of roller compaction on 150mg tablets
◆ 30% HPMC, not RC
■ 500lb/in RC (FP), 40% HPMC
▲ 1000lb/in RC (FP), 40% HPMC
× 1500lb/in RC (FP), 40% HPMC
* CSF, 40% HPMC, not RC
Hardness, kP
35
30
25
20
15
10
5
0
0.00
10.00
20.00
30.00
Comp F, kN

FIG.13

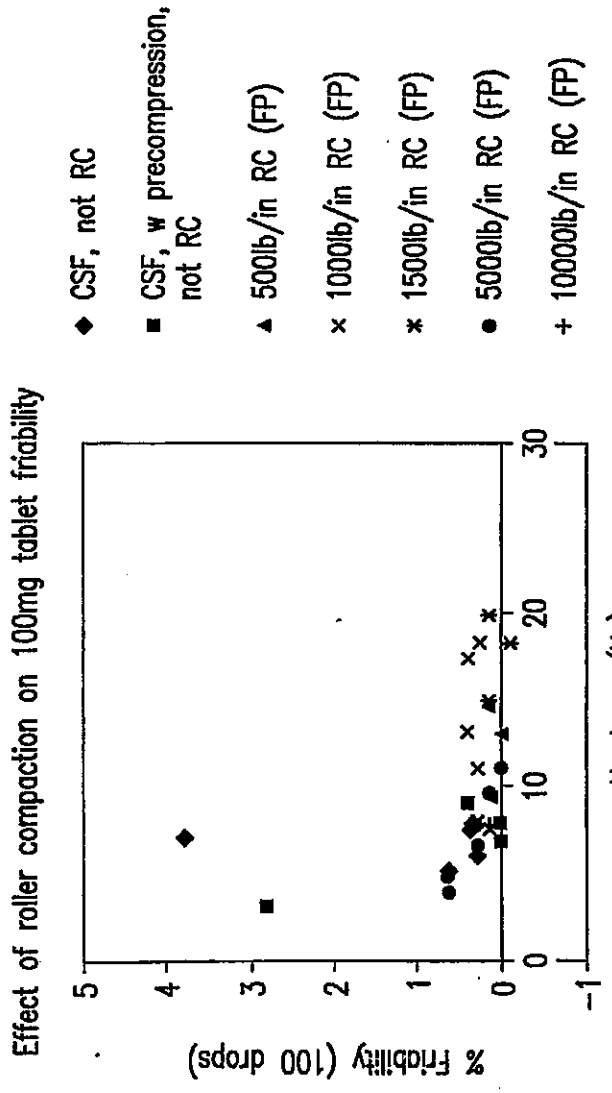

Effect of roller compaction on 100mg tablet friability
% Friability (100 drops)
Hardness (Kp)
5
4
3
2
1
0
-1
0
10
20
30
◆ CSF, not RC
■ CSF, w precompression, not RC
▲ 500lb/in RC (FP)
× 1000lb/in RC (FP)
* 1500lb/in RC (FP)
● 5000lb/in RC (FP)
+ 10000lb/in RC (FP)

FIG.14

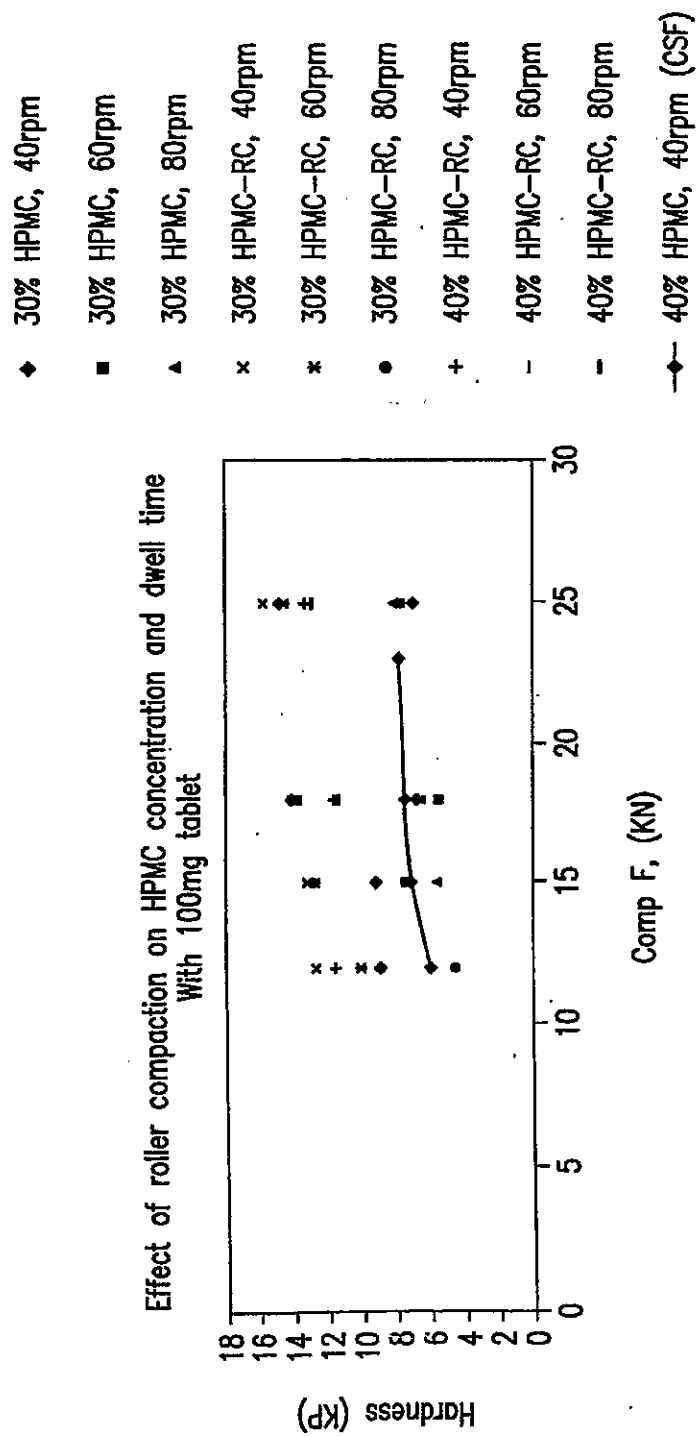

Effect of roller compaction on HPMC concentration and dwell time
With 100mg tablet
Hardness (KP)
Comp F, (KN)
0
2
4
6
8
10
12
14
16
18
0
5
10
15
20
25
30
30% HPMC, 40rpm
30% HPMC, 60rpm
30% HPMC, 80rpm
30% HPMC-RC, 40rpm
30% HPMC-RC, 60rpm
30% HPMC-RC, 80rpm
40% HPMC-RC, 40rpm
40% HPMC-RC, 60rpm
40% HPMC-RC, 80rpm
40% HPMC, 40rpm (CSF)

FIG. 15

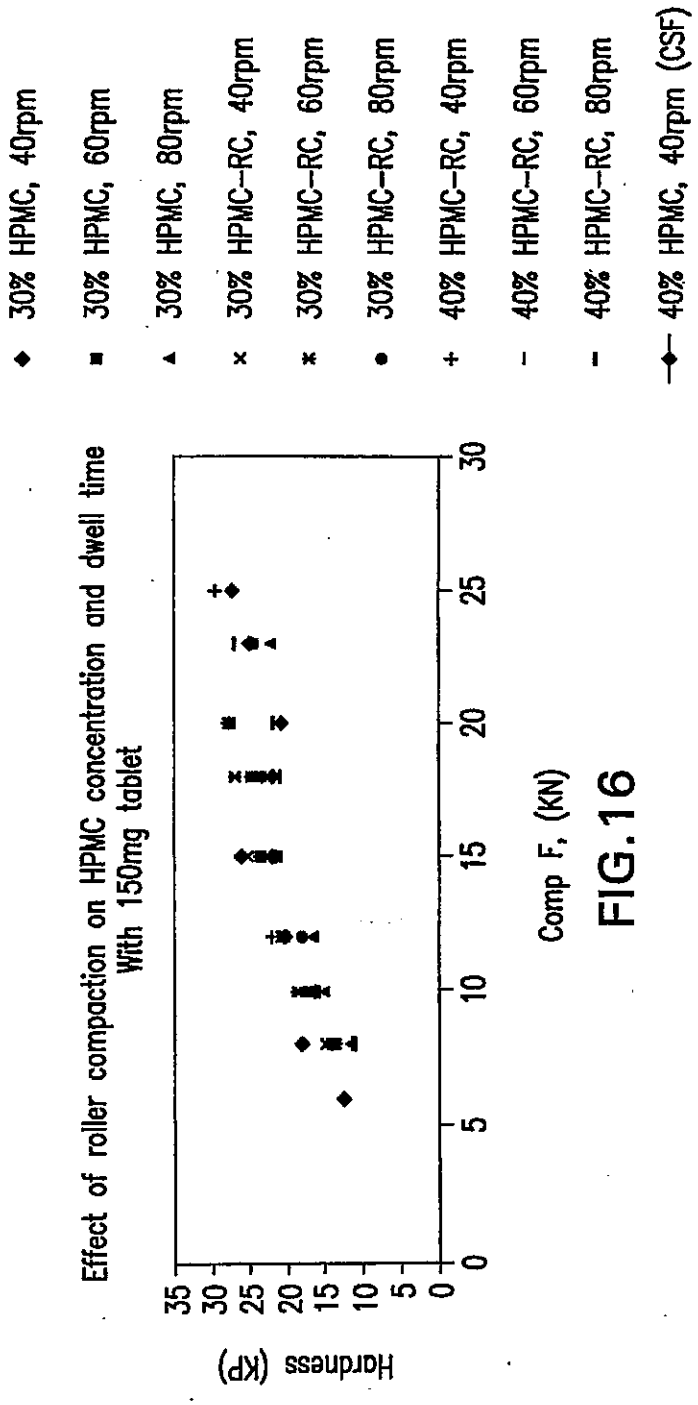

Effect of roller compaction on HPMC concentration and dwell time
With 150mg tablet
Hardness (KP)
Comp F, (KN)
0
5
10
15
20
25
30
35
30% HPMC, 40rpm
30% HPMC, 60rpm
30% HPMC, 80rpm
30% HPMC-RC, 40rpm
30% HPMC-RC, 60rpm
30% HPMC-RC, 80rpm
40% HPMC-RC, 40rpm
40% HPMC-RC, 60rpm
40% HPMC-RC, 80rpm
40% HPMC, 40rpm (CSF)

FIG. 16

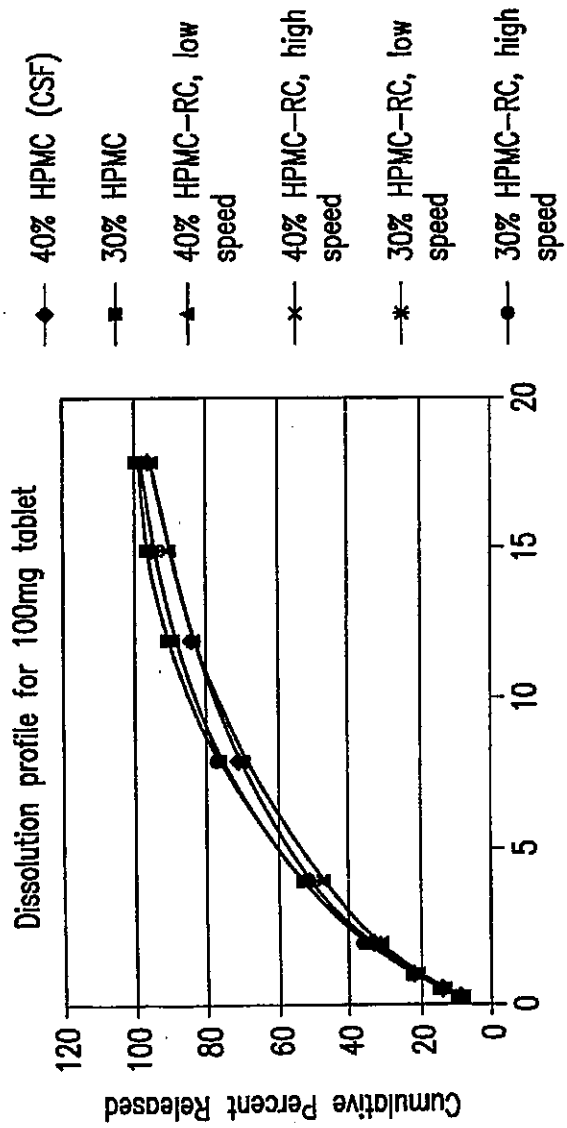

Dissolution profile for 100mg tablet
Cumulative Percent Released
120
100
80
60
40
20
0
0
5
10
15
20
Time (hrs)
40% HPMC (CSF)
30% HPMC
40% HPMC-RC, low speed
40% HPMC-RC, high speed
30% HPMC-RC, low speed
30% HPMC-RC, high speed

FIG. 17

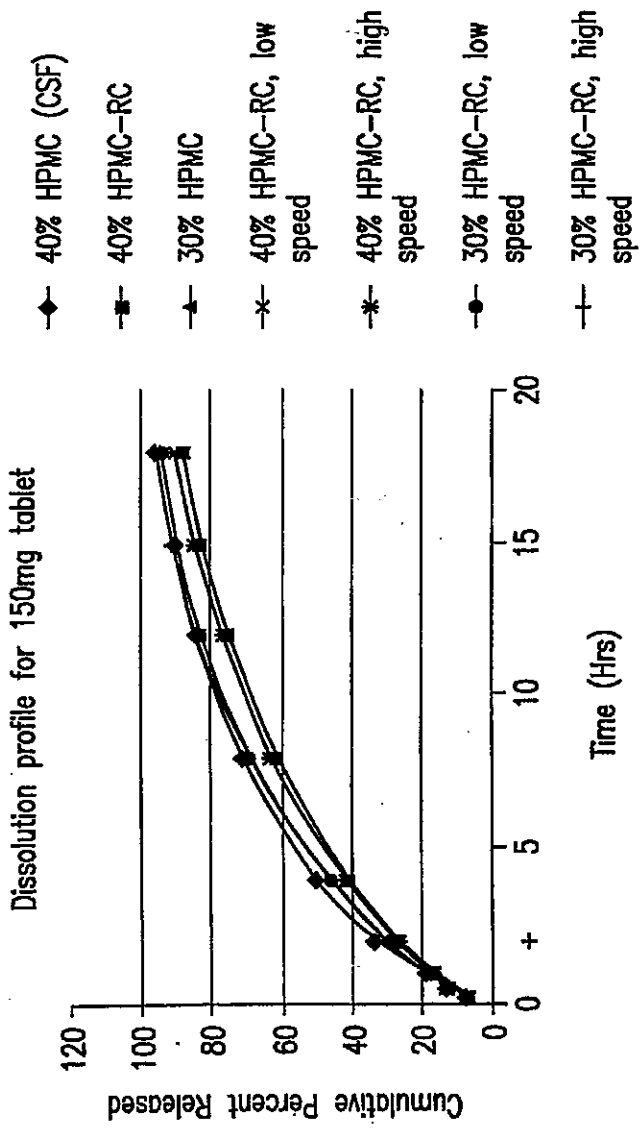

Dissolution profile for 150mg tablet
Cumulative Percent Released
120
100
80
60
40
20
0
0
5
10
15
20
Time (Hrs)
40% HPMC (CSF)
40% HPMC-RC
30% HPMC
40% HPMC-RC, low speed
40% HPMC-RC, high speed
30% HPMC-RC, low speed
30% HPMC-RC, high speed

FIG.18

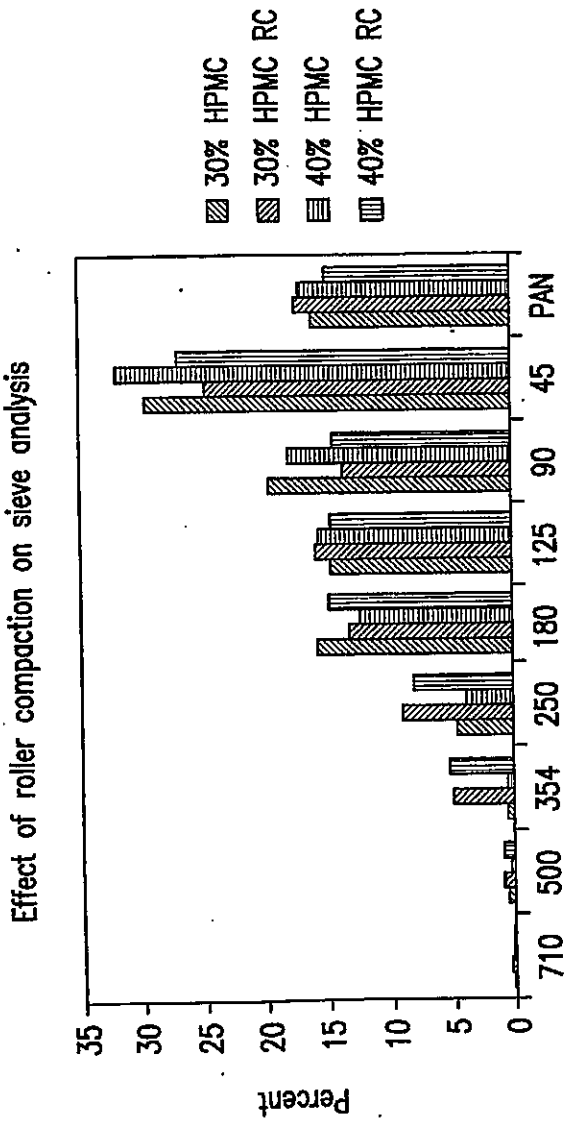

Effect of roller compaction on sieve analysis
30% HPMC
30% HPMC RC
40% HPMC
40% HPMC RC
Percent
0
5
10
15
20
25
30
35
710
500
354
250
180
125
90
45
PAN
Microns

FIG.19

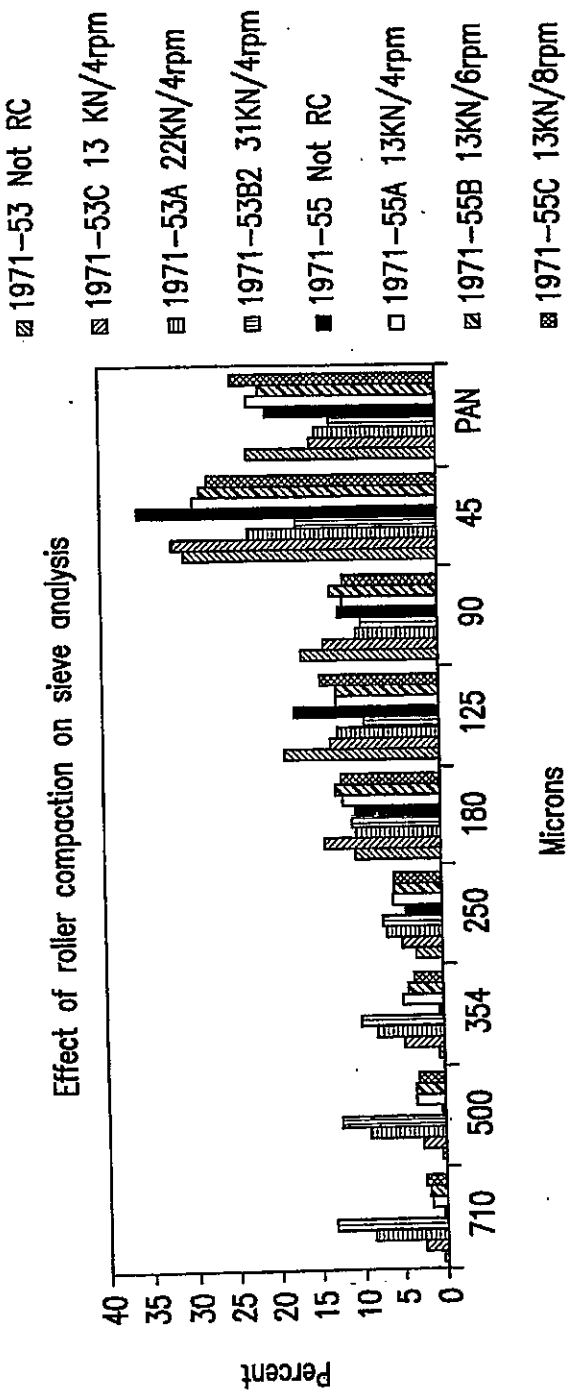

Effect of roller compaction on sieve analysis
1971-53 Not RC
1971-53C 13 KN/4rpm
1971-53A 22KN/4rpm
1971-53B2 31KN/4rpm
1971-55 Not RC
1971-55A 13KN/4rpm
1971-55B 13KN/6rpm
1971-55C 13KN/8rpm
Percent
0
5
10
15
20
25
30
35
40
710
500
354
250
180
125
90
45
PAN
Microns

FIG.20

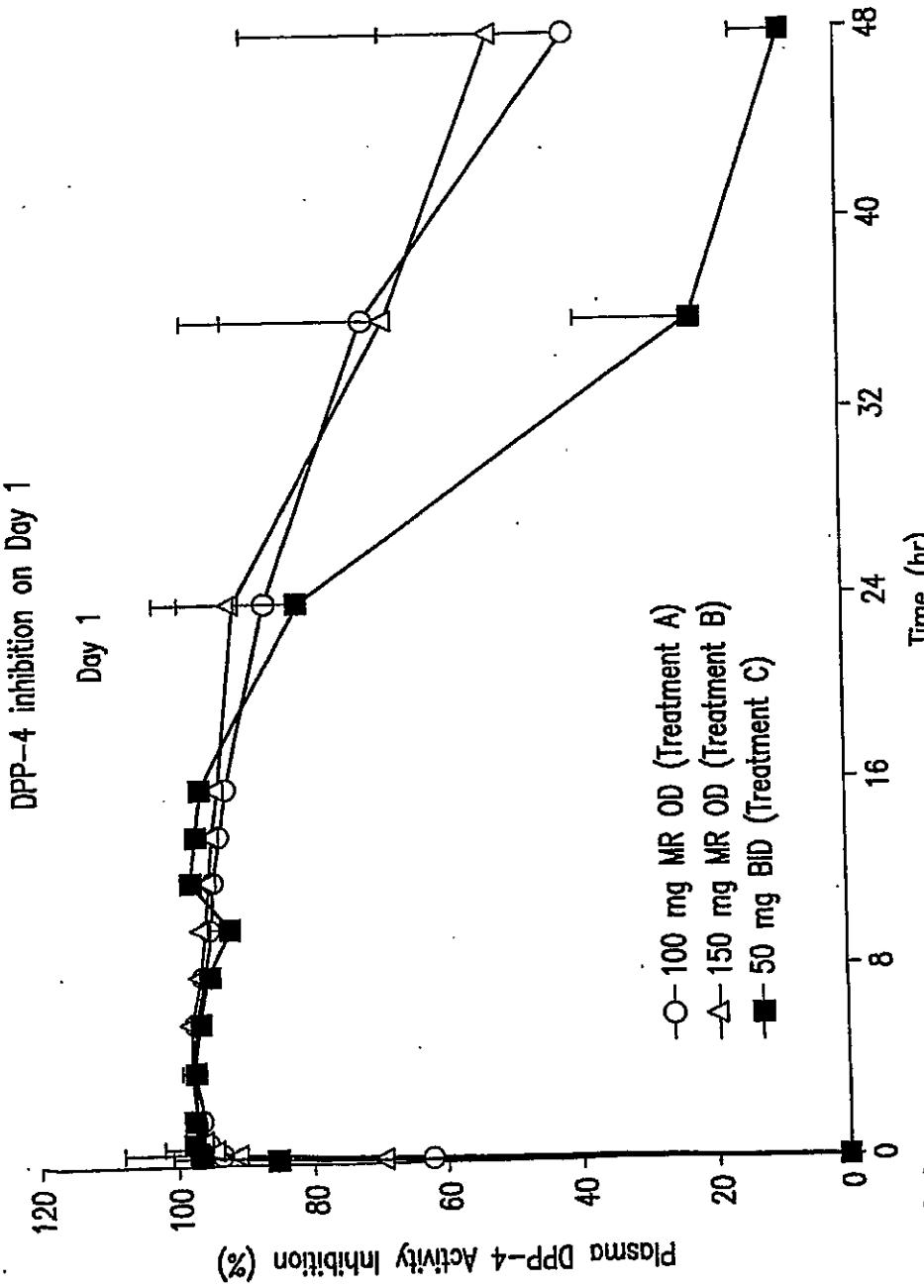

DPP-4 inhibition on Day 1
Day 1
Plasma DPP-4 Activity Inhibition (%)
120
100
80
60
40
20
0
0
8
16
24
32
40
48
Time (hr)
100 mg MR OD (Treatment A)
150 mg MR OD (Treatment B)
50 mg BID (Treatment C)

FIG.21

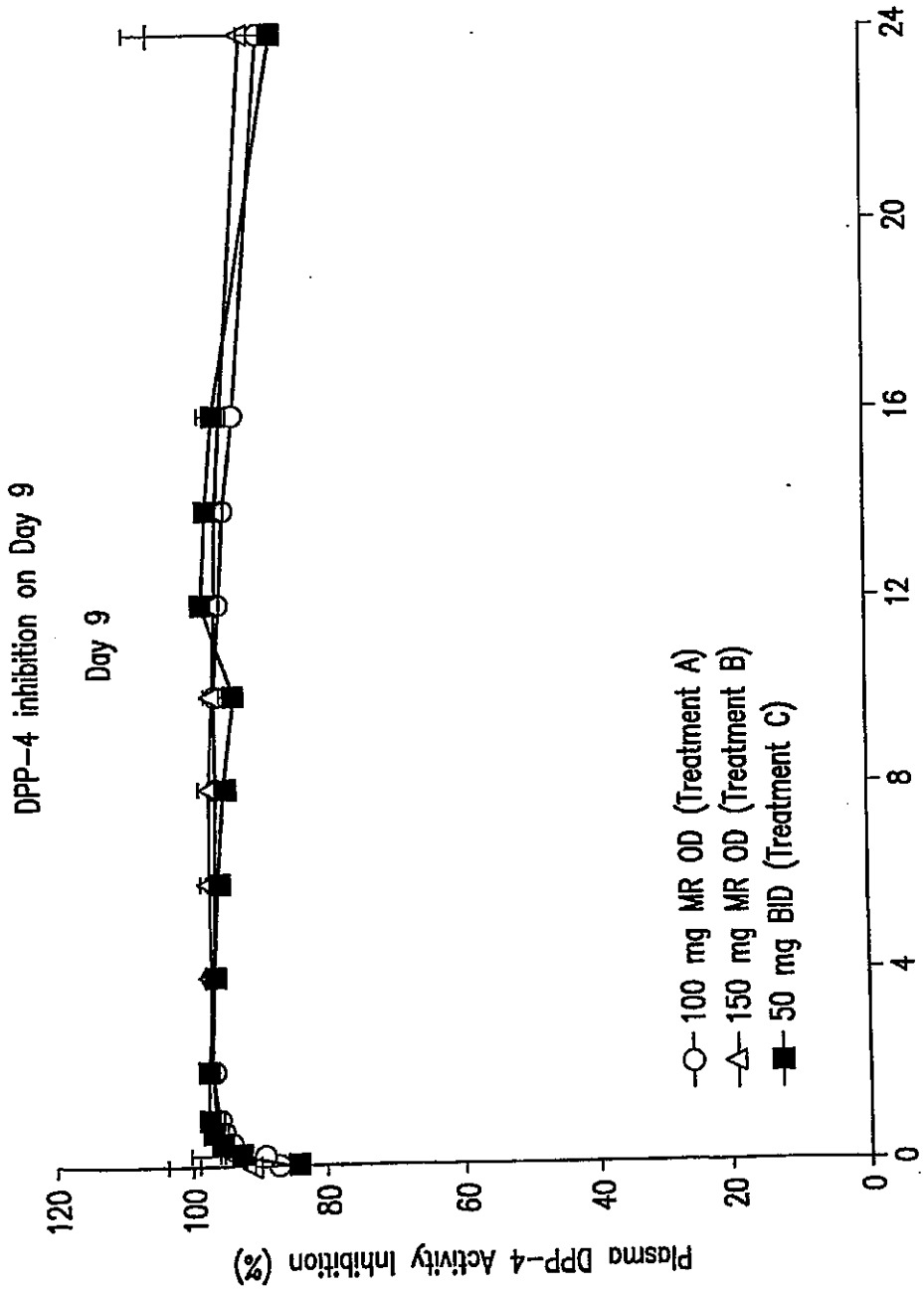

DPP-4 inhibition on Day 9
Day 9
Plasma DPP-4 Activity Inhibition (%)
120
100
80
60
40
20
0
0
4
8
12
16
20
24
Time (hr)
100 mg MR OD (Treatment A)
150 mg MR OD (Treatment B)
50 mg BID (Treatment C)

FIG.22

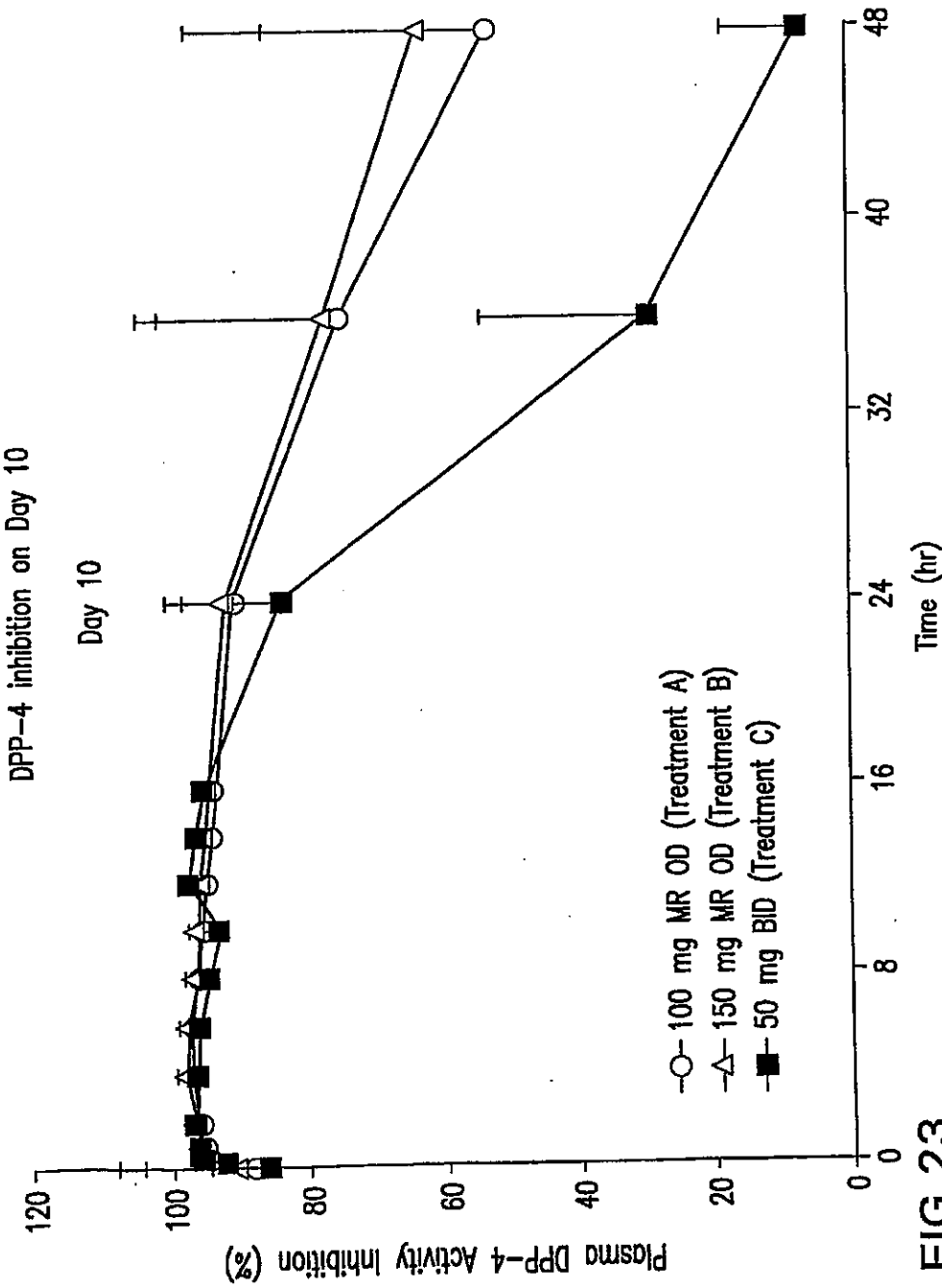

DPP-4 inhibition on Day 10
Day 10
Plasma DPP-4 Activity Inhibition (%)
120
100
80
60
40
20
0
0
8
16
24
32
40
48
Time (hr)
100 mg MR OD (Treatment A)
150 mg MR OD (Treatment B)
50 mg BID (Treatment C)

FIG.23

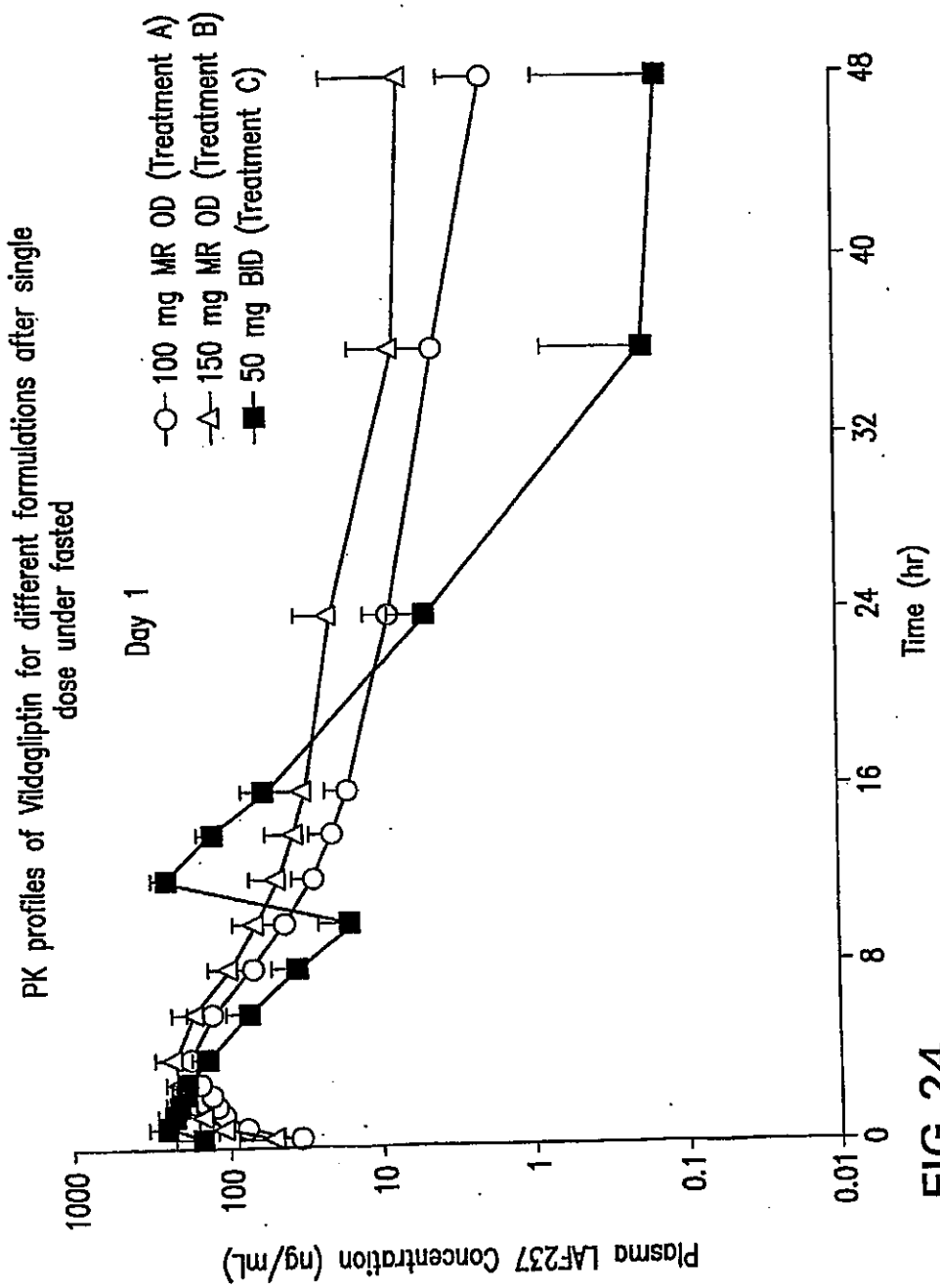

PK profiles of Vildagliptin for different formulations after single dose under fasted
Day 1
100 mg MR OD (Treatment A)
150 mg MR OD (Treatment B)
50 mg BID (Treatment C)
Plasma LAF237 Concentration (ng/mL)
1000
100
10
1
0.1
0.01
0
8
16
24
32
40
48
Time (hr)

FIG.24

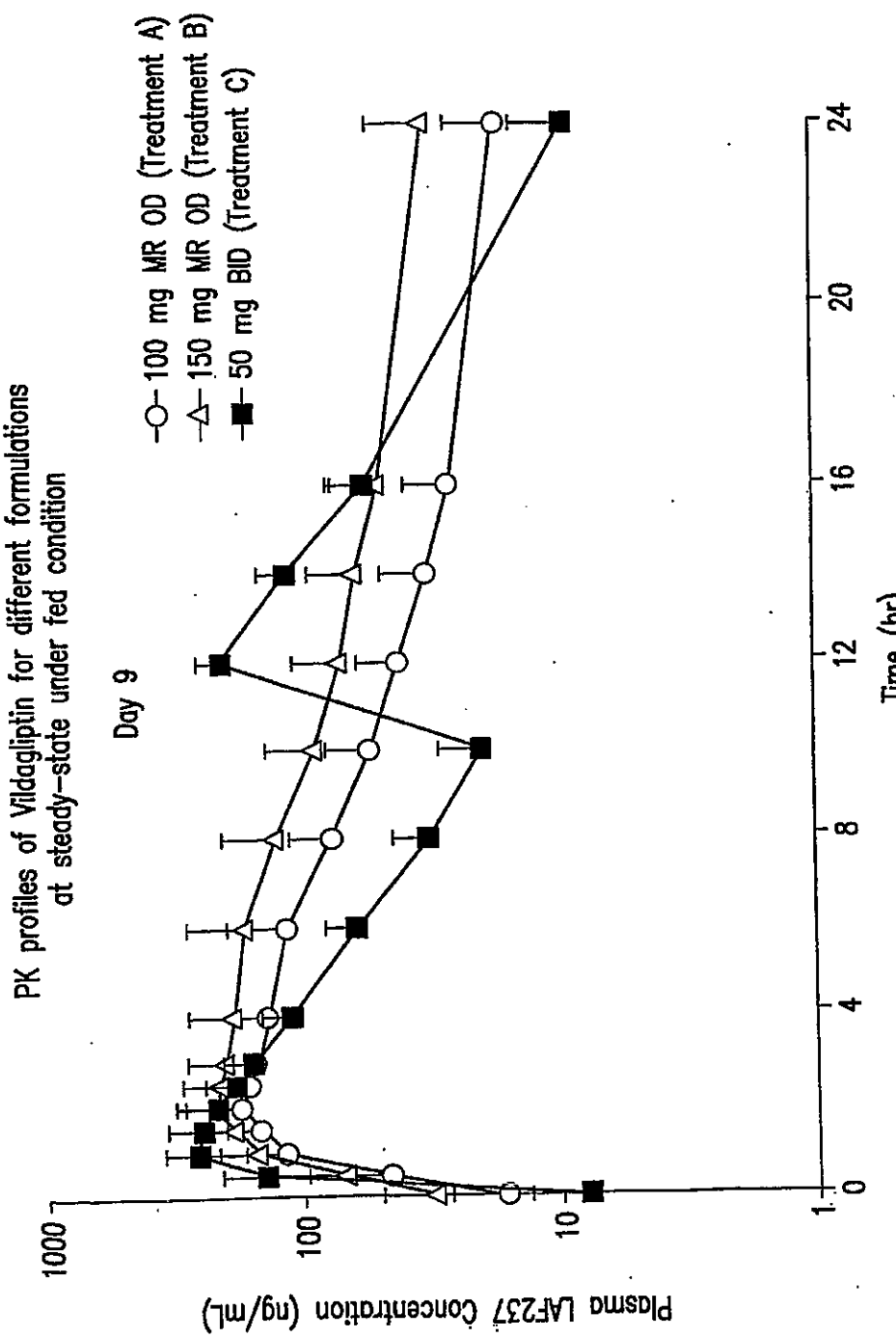

PK profiles of Vildagliptin for different formulations
at steady-state under fed condition
Day 9
100 mg MR OD (Treatment A)
150 mg MR OD (Treatment B)
50 mg BID (Treatment C)
Plasma LAF237 Concentration (ng/mL)
1000
100
10
1
0
4
8
12
16
20
24
Time (hr)

FIG.25

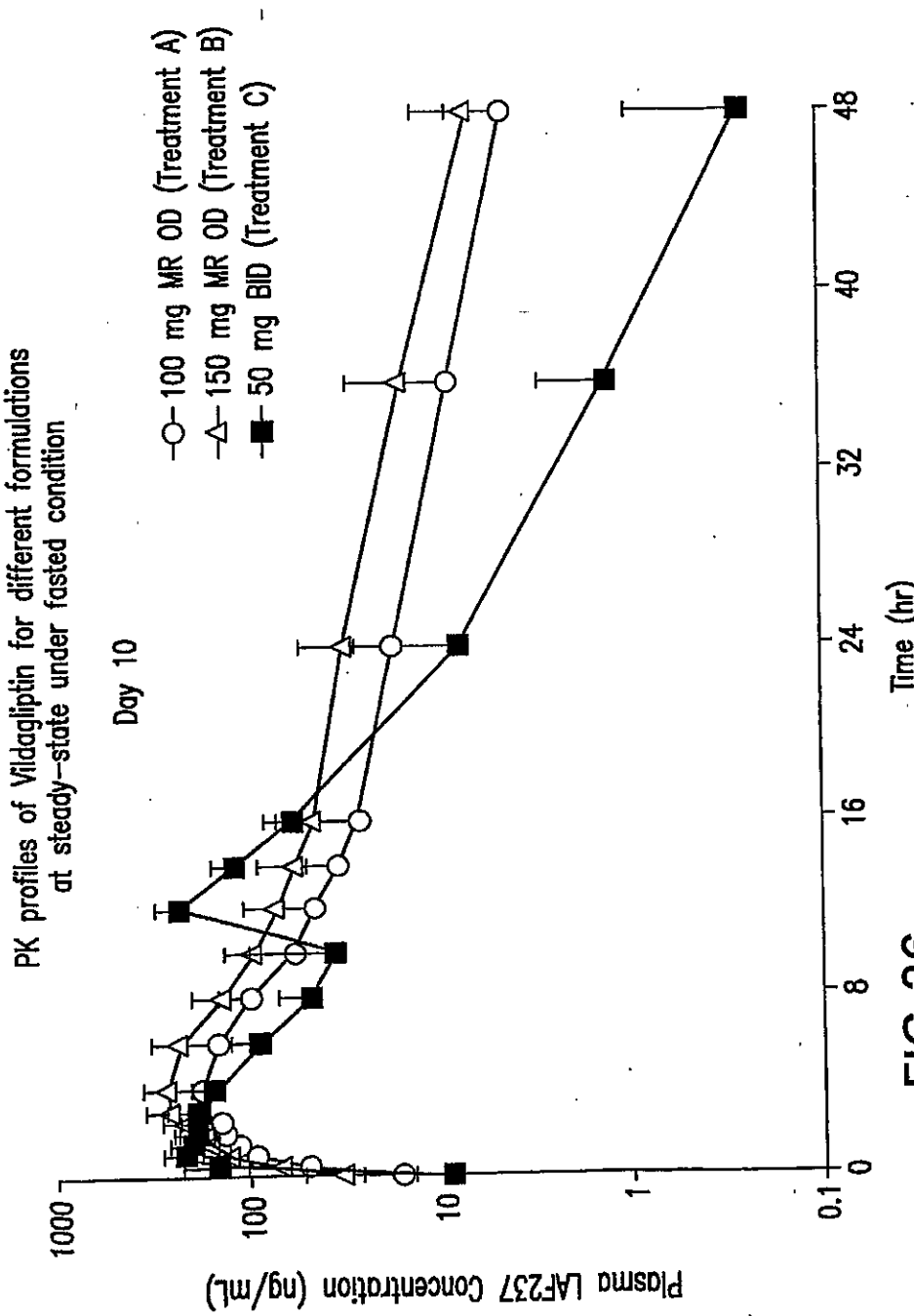

PK profiles of Vildagliptin for different formulations
at steady-state under fasted condition
Day 10
100 mg MR OD (Treatment A)
150 mg MR OD (Treatment B)
50 mg BID (Treatment C)
Plasma LAF237 Concentration (ng/mL)
1000
100
10
1
0.1
0
8
16
24
32
40
48
Time (hr)

FIG.26