FIG. 1A

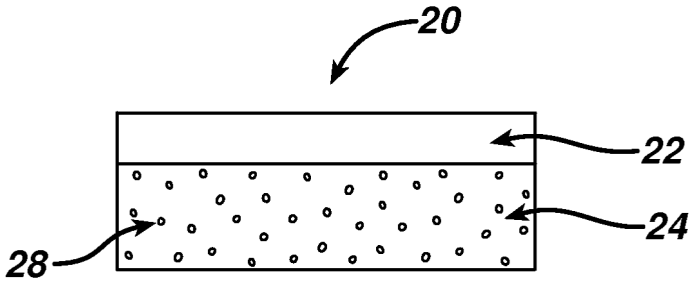


FIG. 1B

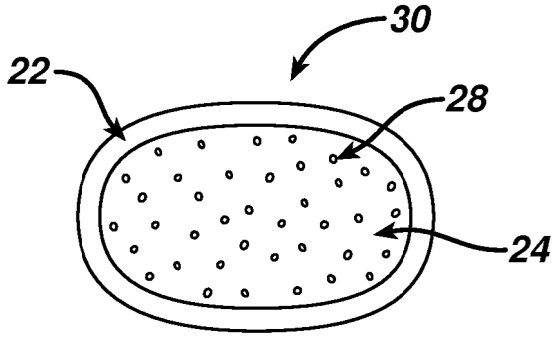


FIG. 1C

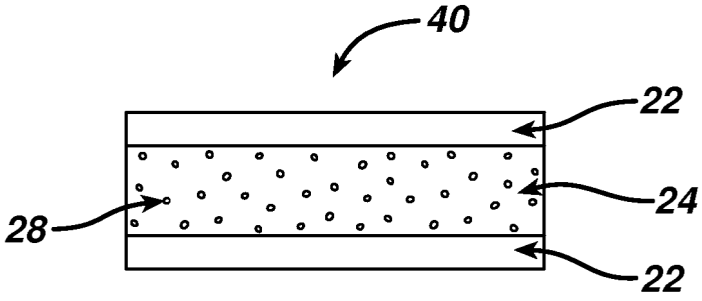


FIG. 2

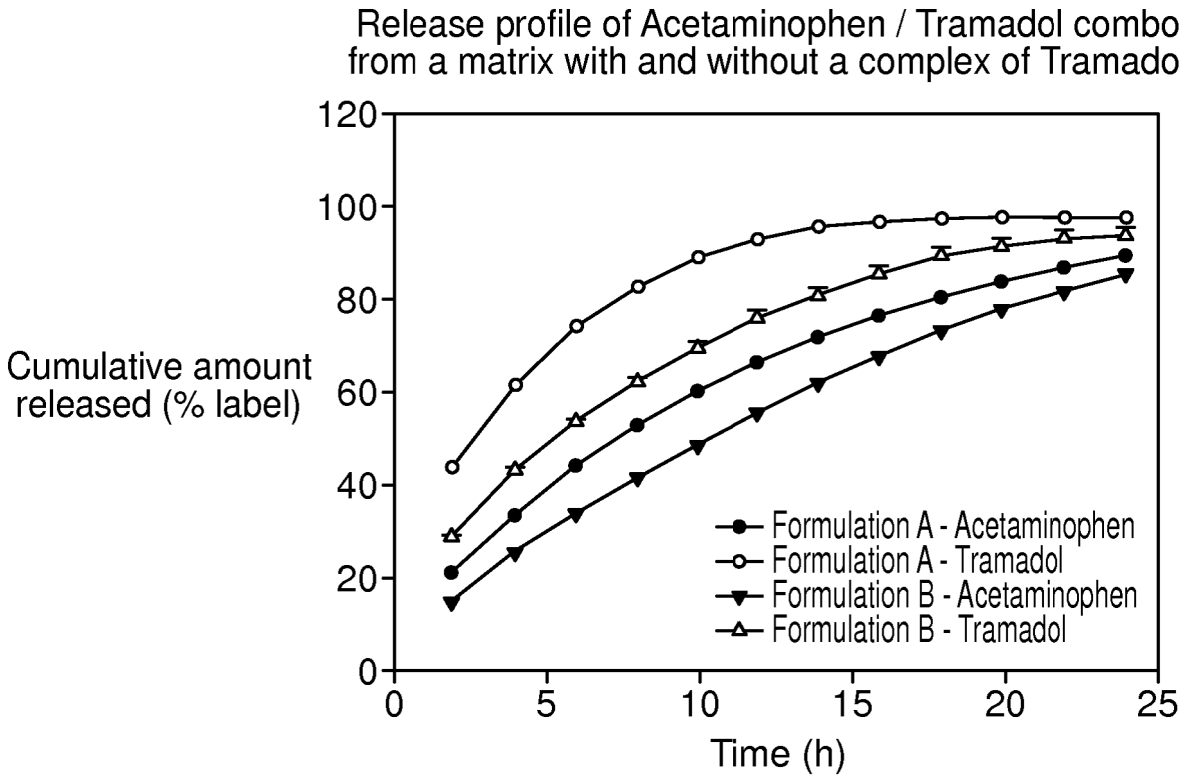

Release profile of Acetaminophen / Tramadol combo from a matrix with and without a complex of Tramadol
Cumulative amount released (% label)
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)
Formulation A - Acetaminophen
Formulation A - Tramadol
Formulation B - Acetaminophen
Formulation B - Tramadol

FIG. 3

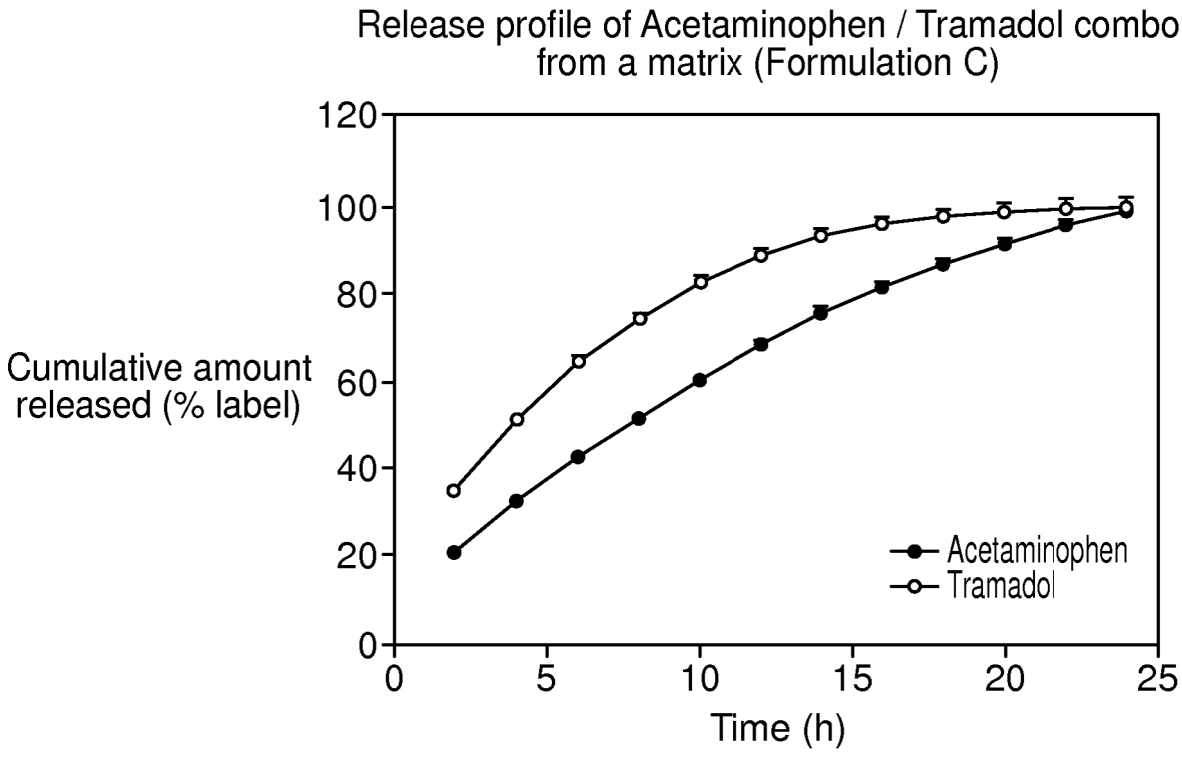

Release profile of Acetaminophen / Tramadol combo from a matrix (Formulation C)
Cumulative amount released (% label)
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)
Acetaminophen
Tramadol

FIG. 4

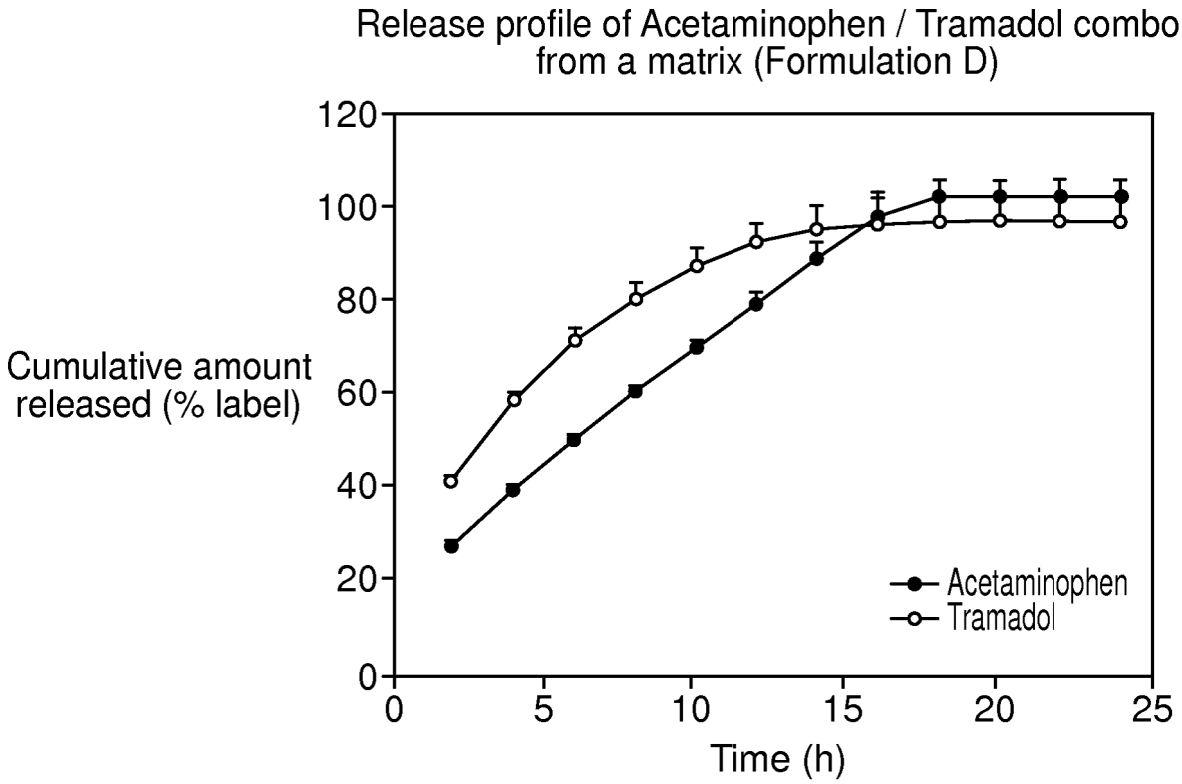

Release profile of Acetaminophen / Tramadol combo from a matrix (Formulation D)
Cumulative amount released (% label)
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)
Acetaminophen
Tramadol

FIG. 5

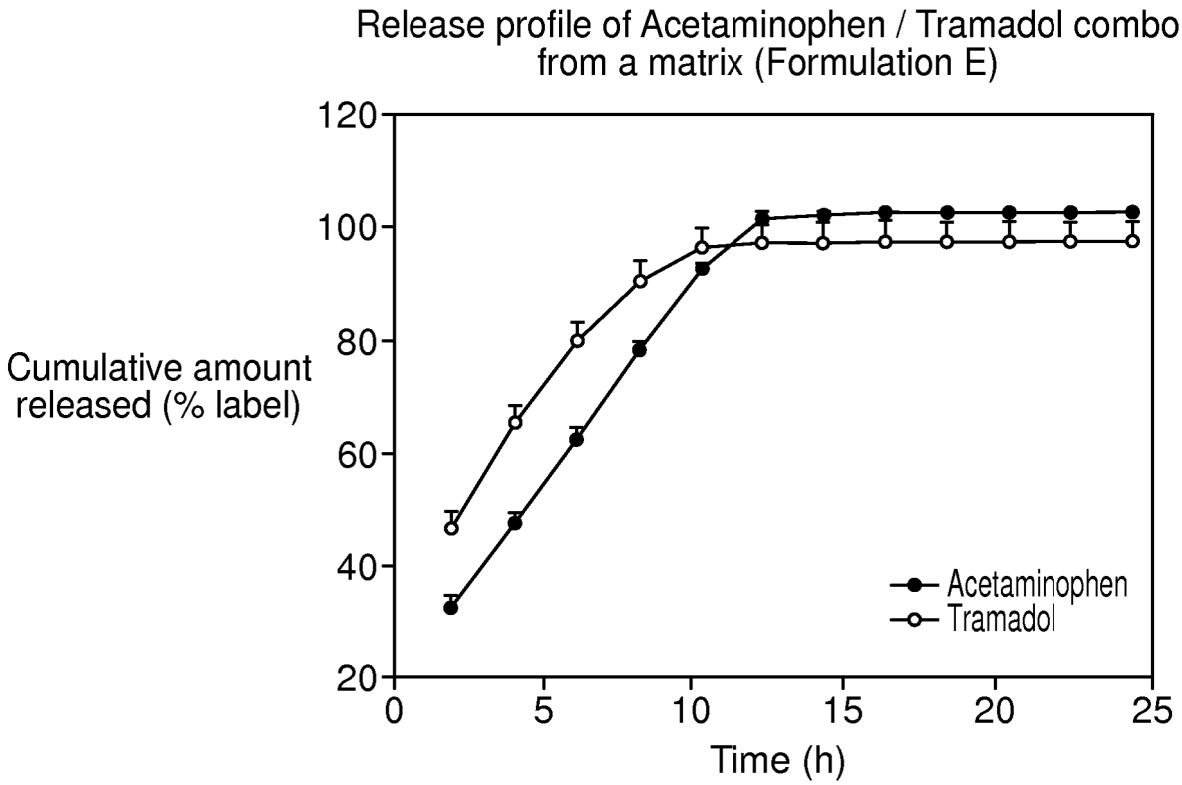

Release profile of Acetaminophen / Tramadol combo from a matrix (Formulation E)
Cumulative amount released (% label)
120
100
80
60
40
20
0
5
10
15
20
25
Time (h)
Acetaminophen
Tramadol

FIG. 6

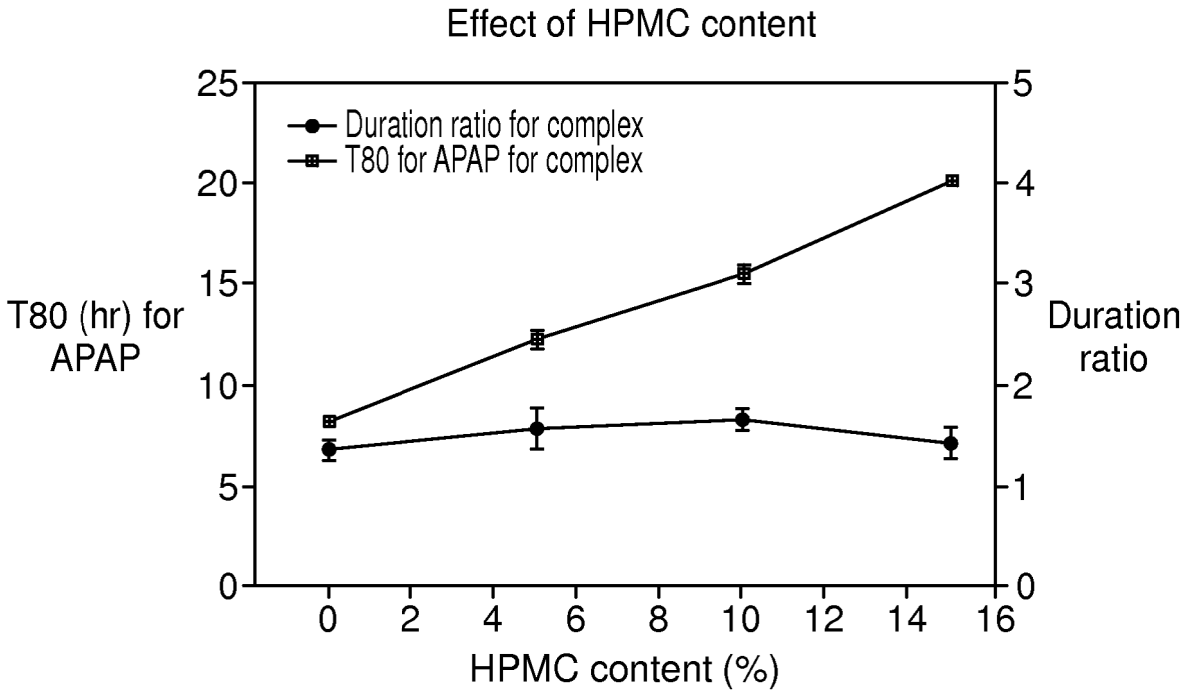

Effect of HPMC content
Duration ratio for complex
T80 for APAP for complex
T80 (hr) for APAP
Duration ratio
HPMC content (%)
0
5
10
15
20
25
0
1
2
3
4
5
0
2
4
6
8
10
12
14
16

FIG. 7a

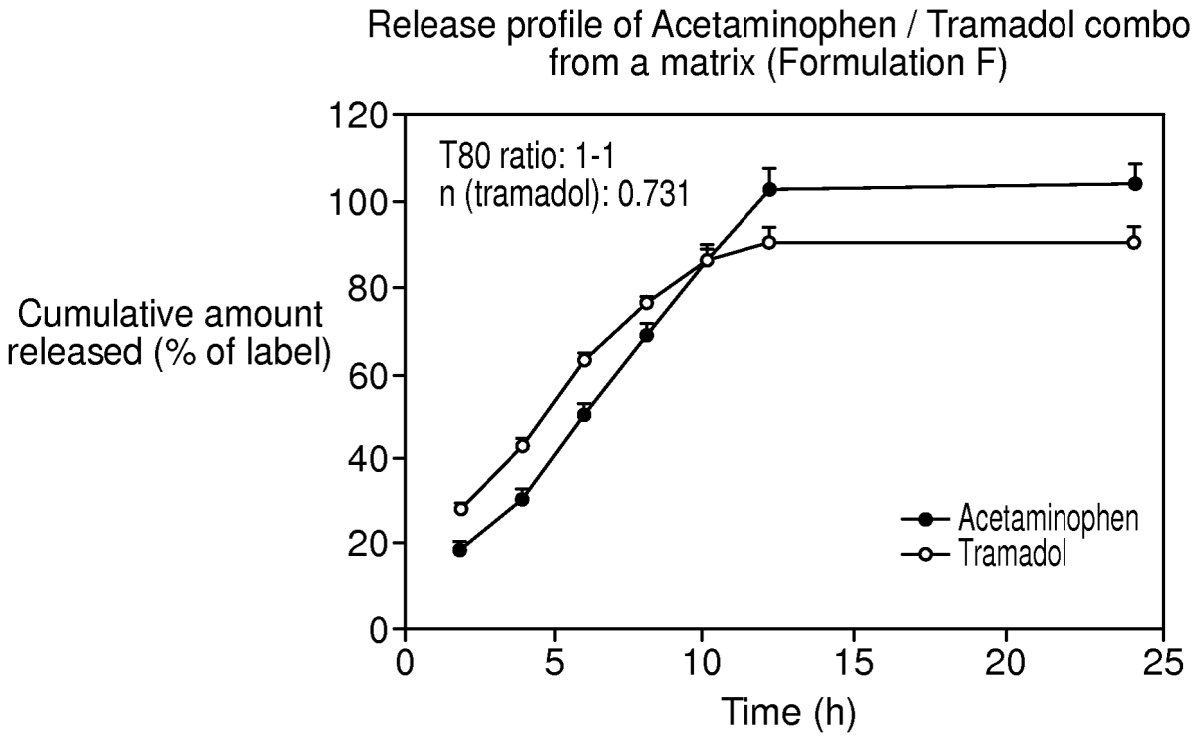

Release profile of Acetaminophen / Tramadol combo from a matrix (Formulation F)
T80 ratio: 1-1
n (tramadol): 0.731
Cumulative amount released (% of label)
Time (h)
Acetaminophen
Tramadol
0
20
40
60
80
100
120
0
5
10
15
20
25

FIG. 7b

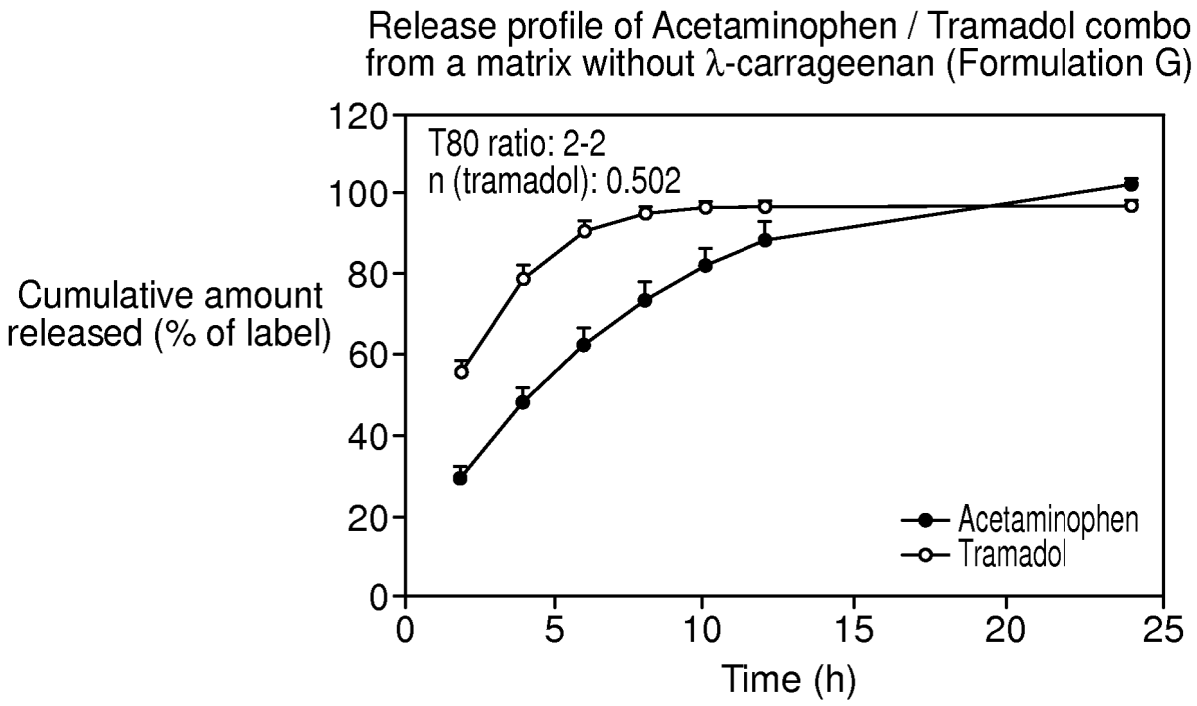

Release profile of Acetaminophen / Tramadol combo
from a matrix without λ-carrageenan (Formulation G)
T80 ratio: 2-2
n (tramadol): 0.502
Cumulative amount released (% of label)
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)
Acetaminophen
Tramadol

FIG. 8

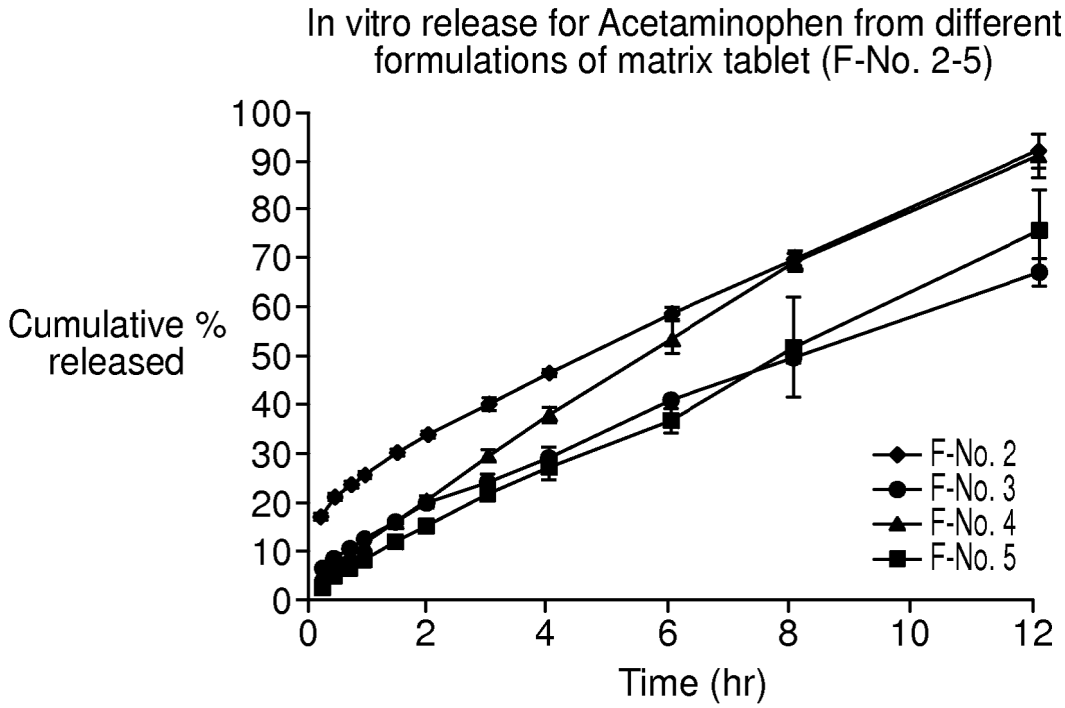

In vitro release for Acetaminophen from different formulations of matrix tablet (F-No. 2-5)
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 2
F-No. 3
F-No. 4
F-No. 5

FIG. 9

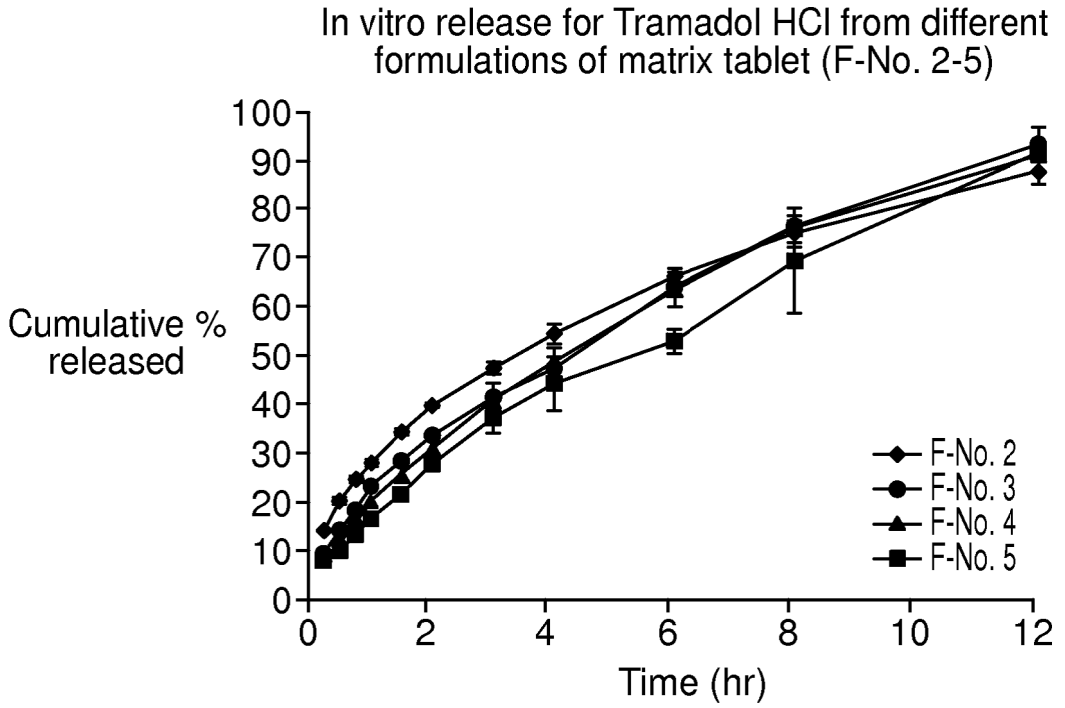

In vitro release for Tramadol HCl from different formulations of matrix tablet (F-No. 2-5)
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 2
F-No. 3
F-No. 4
F-No. 5

FIG. 10

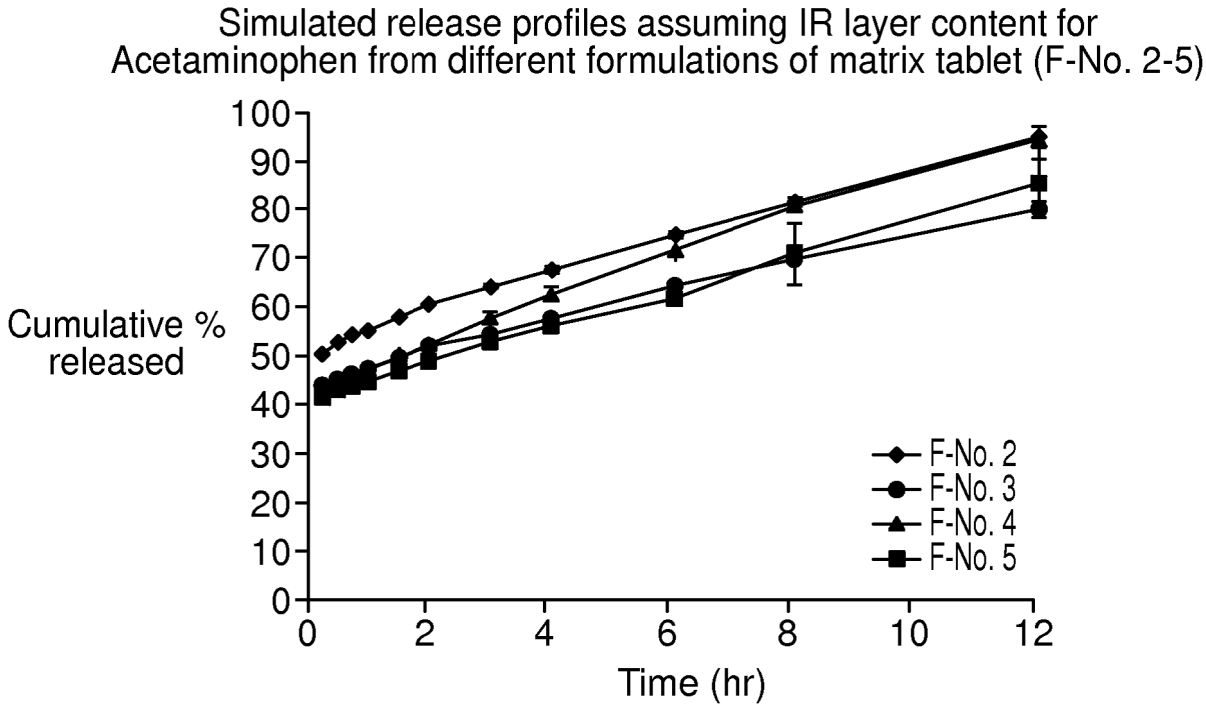

Simulated release profiles assuming IR layer content for
Acetaminophen from different formulations of matrix tablet (F-No. 2-5)
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 2
F-No. 3
F-No. 4
F-No. 5

FIG. 11

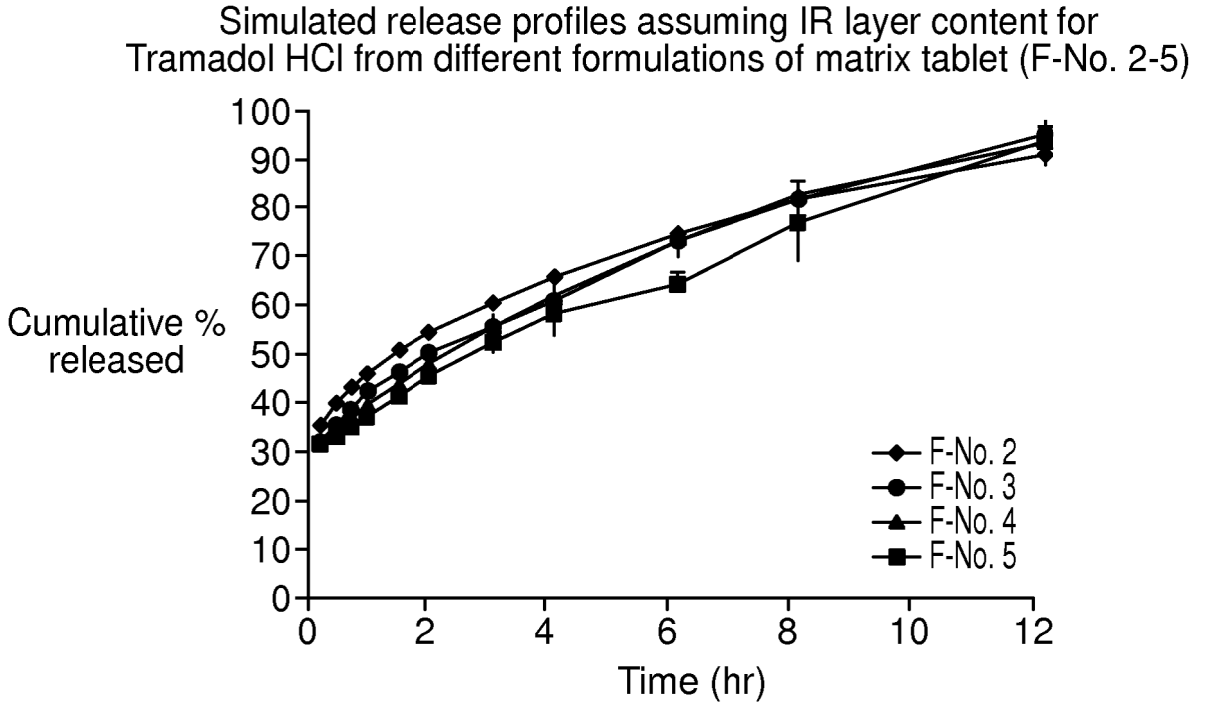

Simulated release profiles assuming IR layer content for
Tramadol HCl from different formulations of matrix tablet (F-No. 2-5)
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 2
F-No. 3
F-No. 4
F-No. 5

FIG. 12

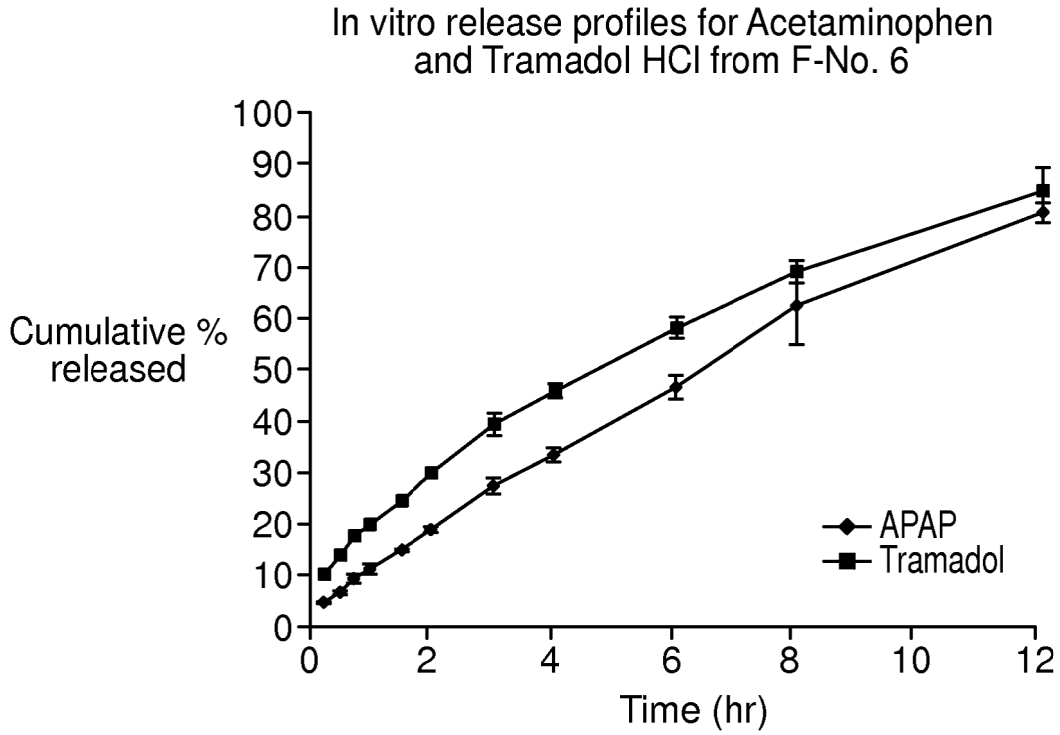

In vitro release profiles for Acetaminophen and Tramadol HCl from F-No. 6
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
APAP
Tramadol

FIG. 13

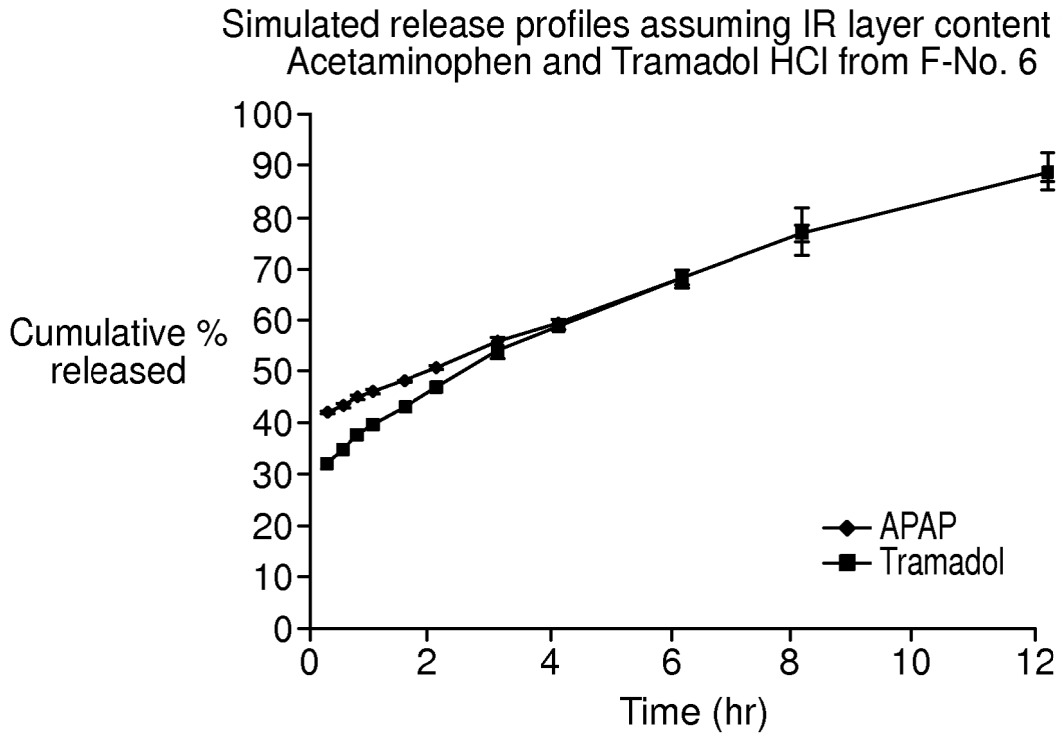

Simulated release profiles assuming IR layer content for Acetaminophen and Tramadol HCl from F-No. 6
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
APAP
Tramadol

FIG. 14

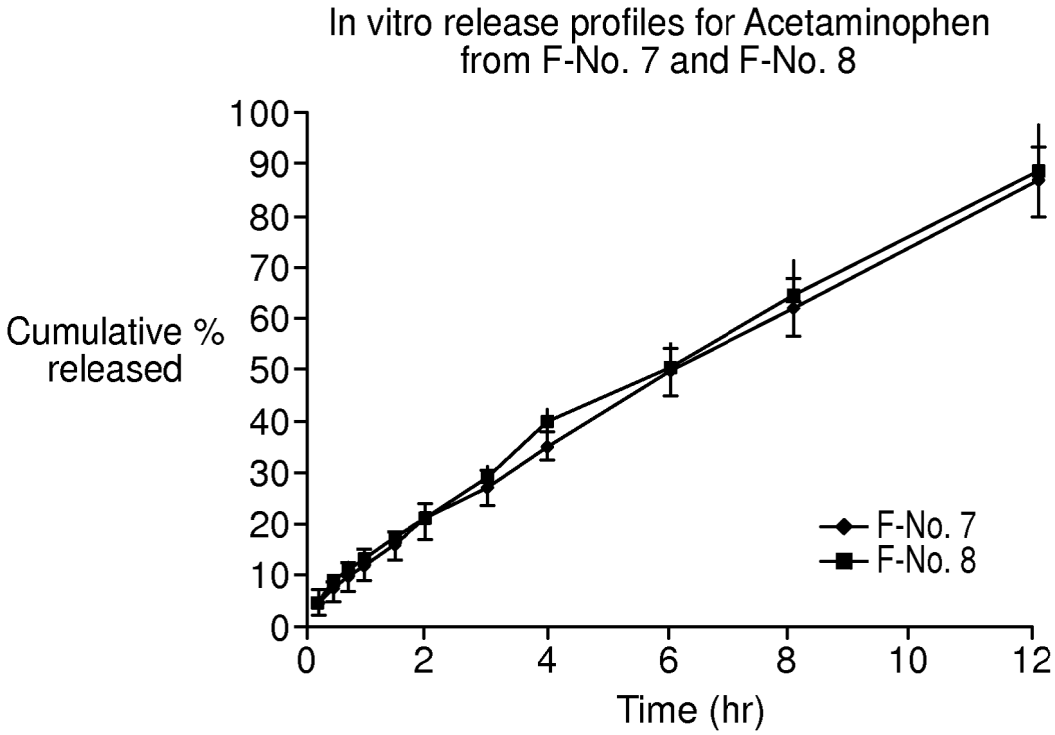

In vitro release profiles for Acetaminophen
from F-No. 7 and F-No. 8
Cumulative %
released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 7
F-No. 8

FIG. 15

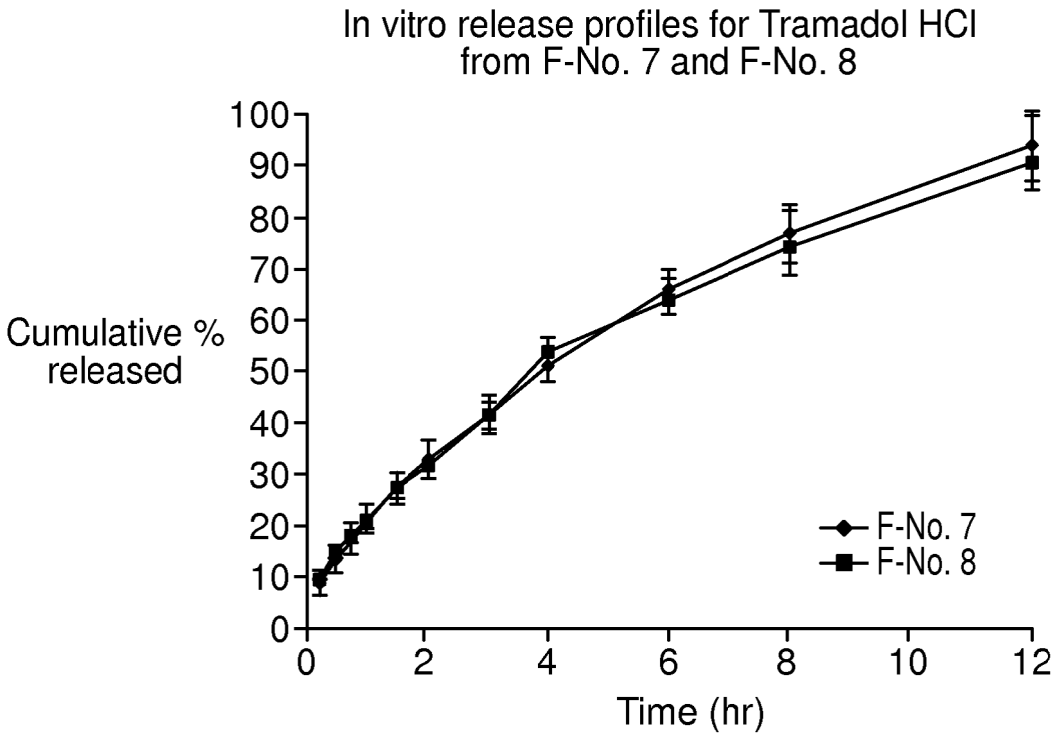

In vitro release profiles for Tramadol HCl
from F-No. 7 and F-No. 8
Cumulative %
released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 7
F-No. 8

FIG. 16

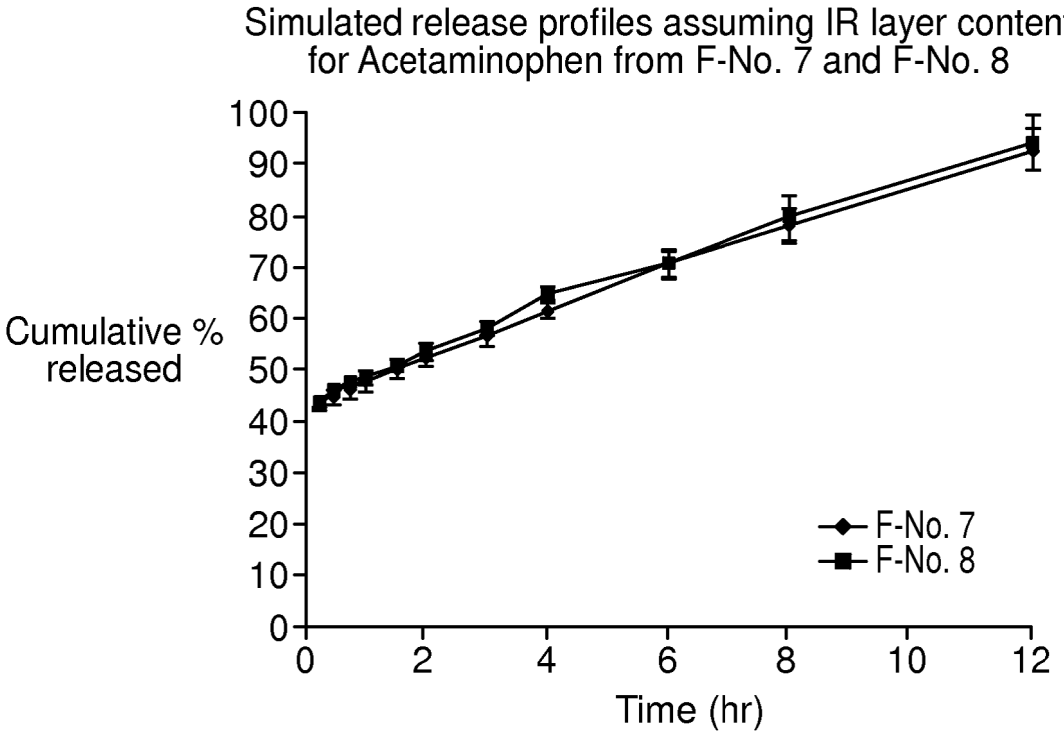

Simulated release profiles assuming IR layer content
for Acetaminophen from F-No. 7 and F-No. 8
Cumulative %
released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 7
F-No. 8

FIG. 17

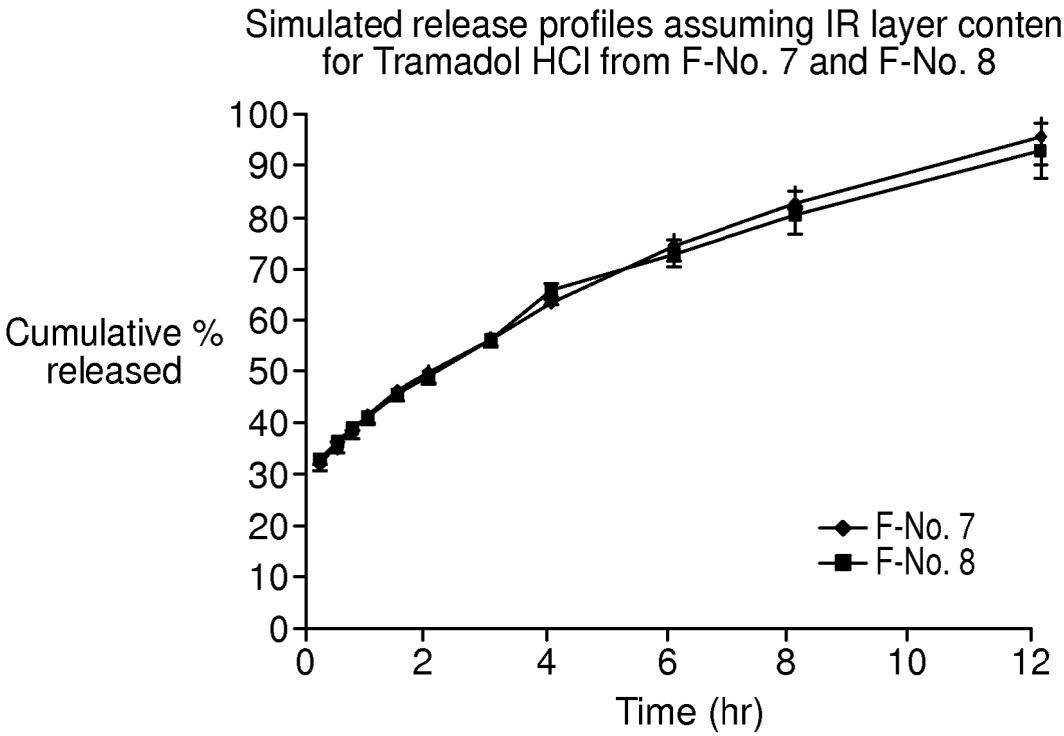

Simulated release profiles assuming IR layer content
for Tramadol HCl from F-No. 7 and F-No. 8
Cumulative %
released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 7
F-No. 8

FIG. 18

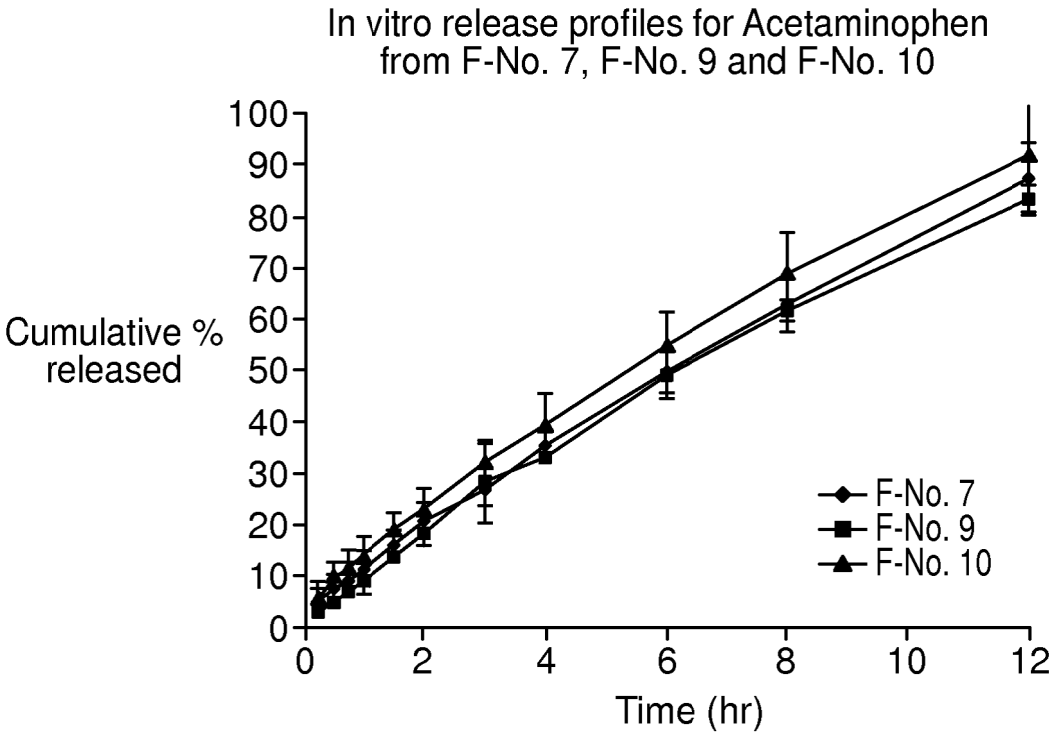

In vitro release profiles for Acetaminophen
from F-No. 7, F-No. 9 and F-No. 10
Cumulative %
released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 7
F-No. 9
F-No. 10

FIG. 19

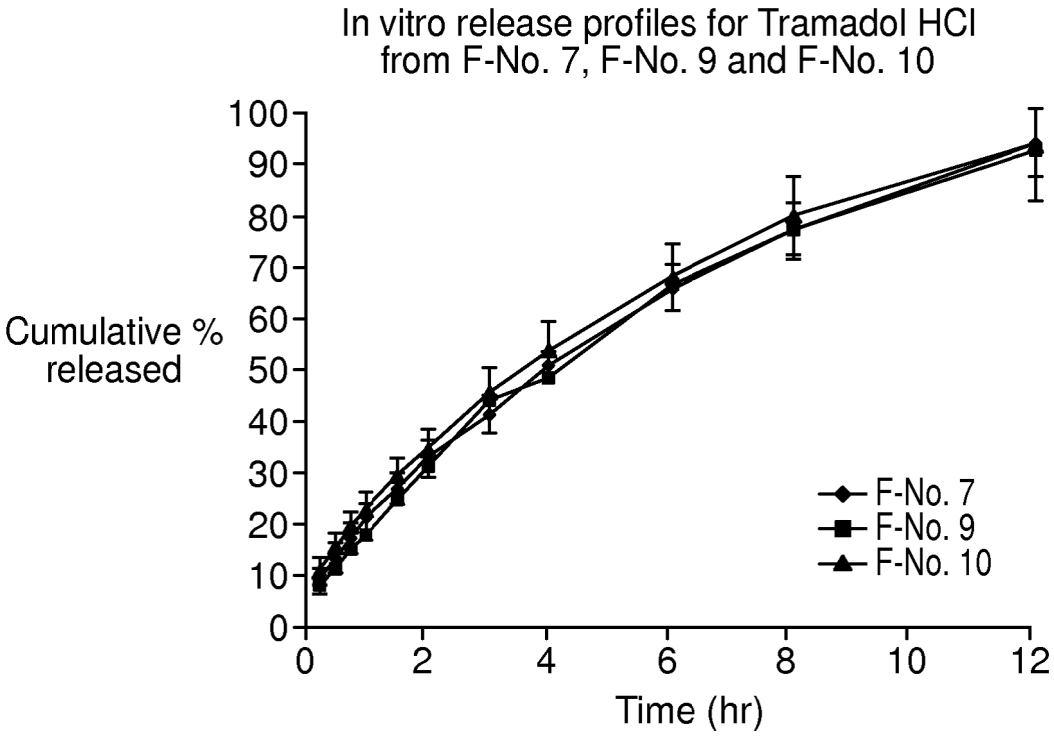

In vitro release profiles for Tramadol HCl
from F-No. 7, F-No. 9 and F-No. 10
Cumulative %
released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 7
F-No. 9
F-No. 10

FIG. 20

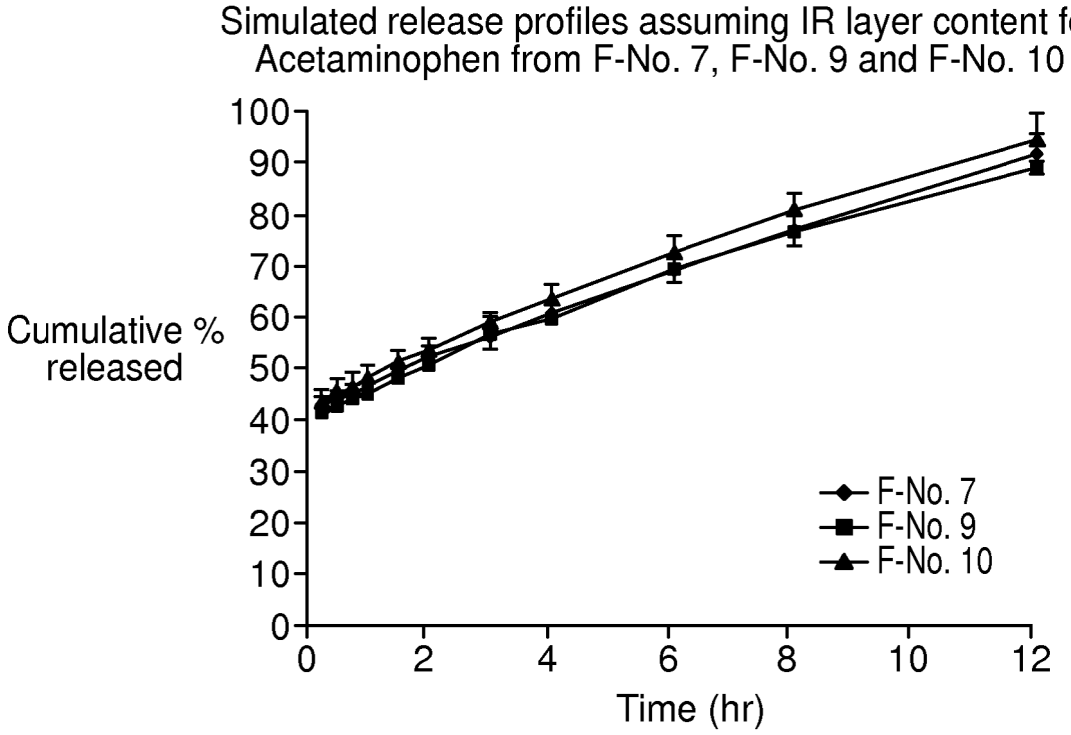

Simulated release profiles assuming IR layer content for Acetaminophen from F-No. 7, F-No. 9 and F-No. 10
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 7
F-No. 9
F-No. 10

FIG. 21

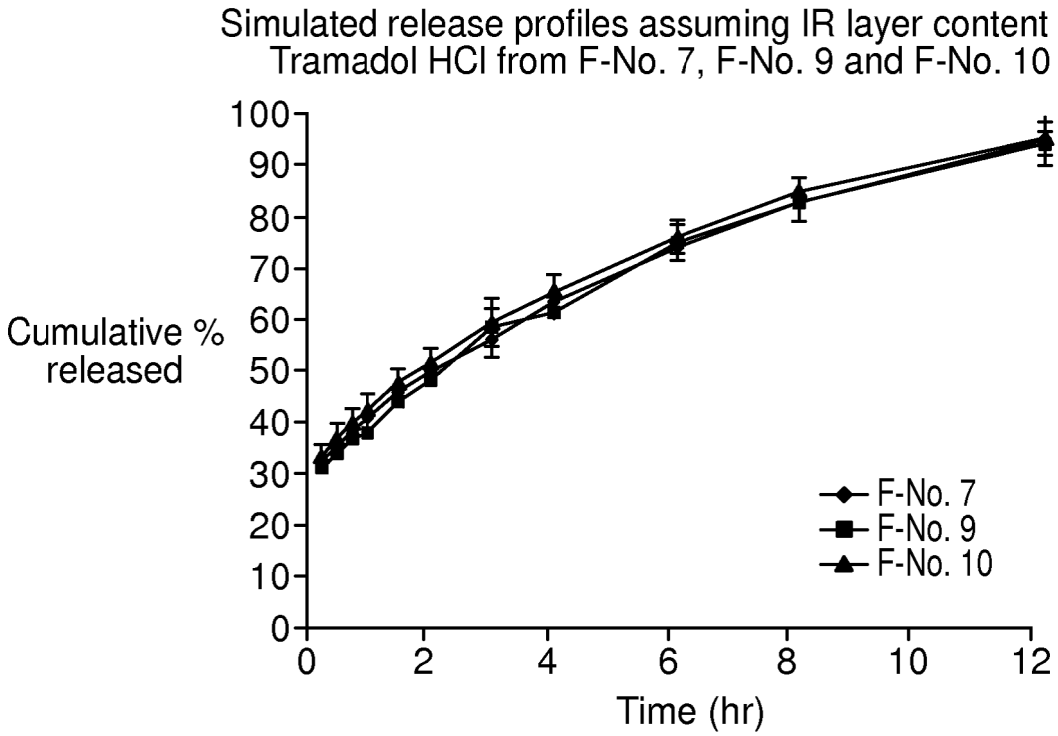

Simulated release profiles assuming IR layer content for Tramadol HCl from F-No. 7, F-No. 9 and F-No. 10
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 7
F-No. 9
F-No. 10

FIG. 22

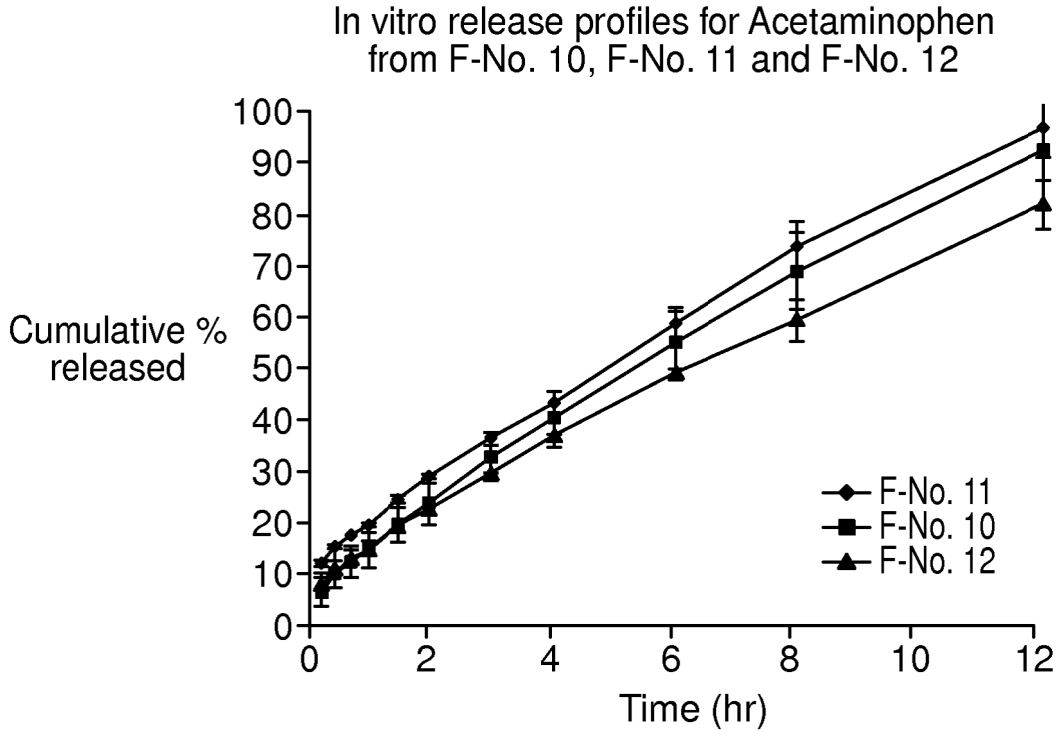

In vitro release profiles for Acetaminophen
from F-No. 10, F-No. 11 and F-No. 12
Cumulative %
released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 11
F-No. 10
F-No. 12

FIG. 23

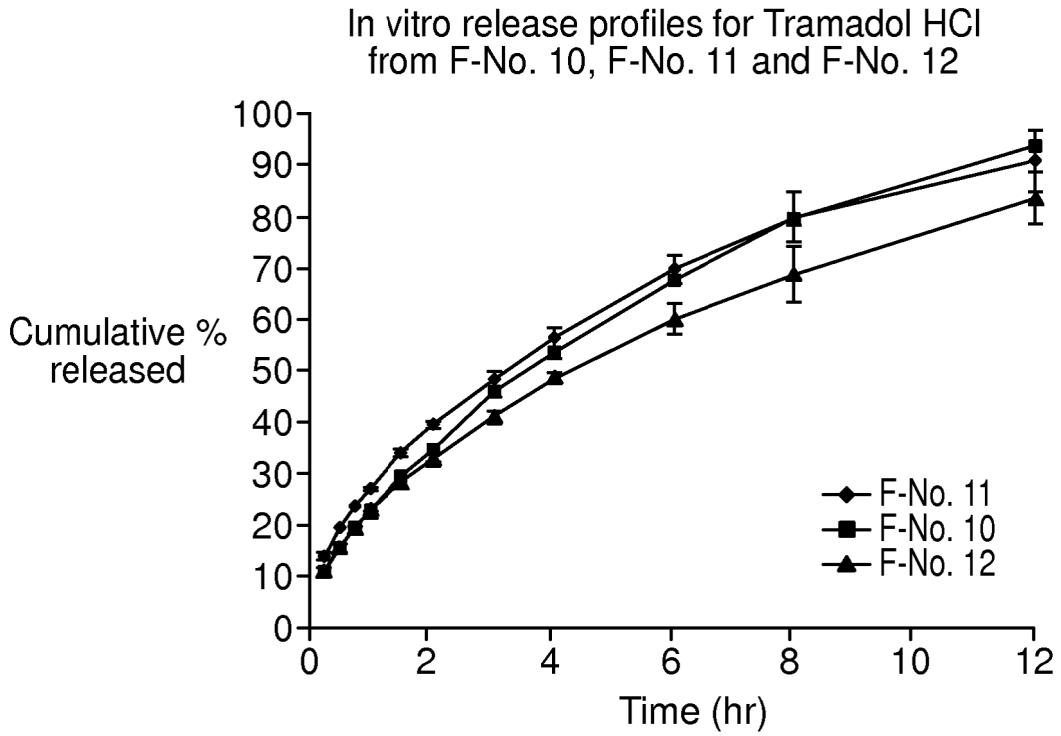

In vitro release profiles for Tramadol HCl
from F-No. 10, F-No. 11 and F-No. 12
Cumulative %
released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 11
F-No. 10
F-No. 12

FIG. 24

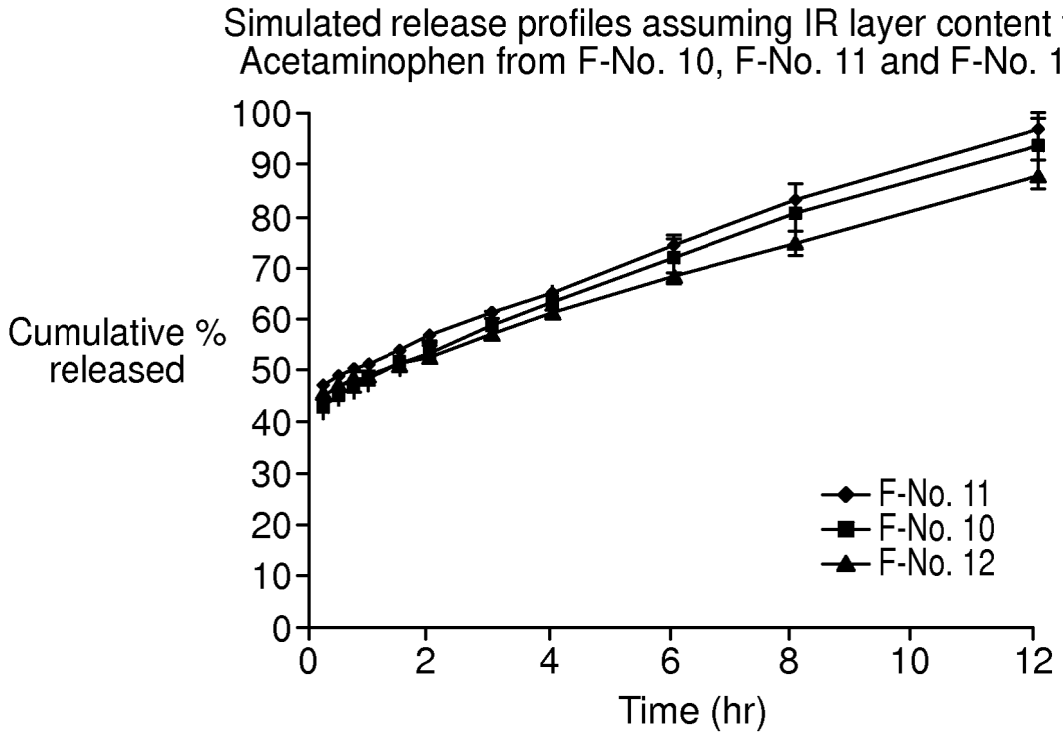

Simulated release profiles assuming IR layer content for Acetaminophen from F-No. 10, F-No. 11 and F-No. 12
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 11
F-No. 10
F-No. 12

FIG. 25

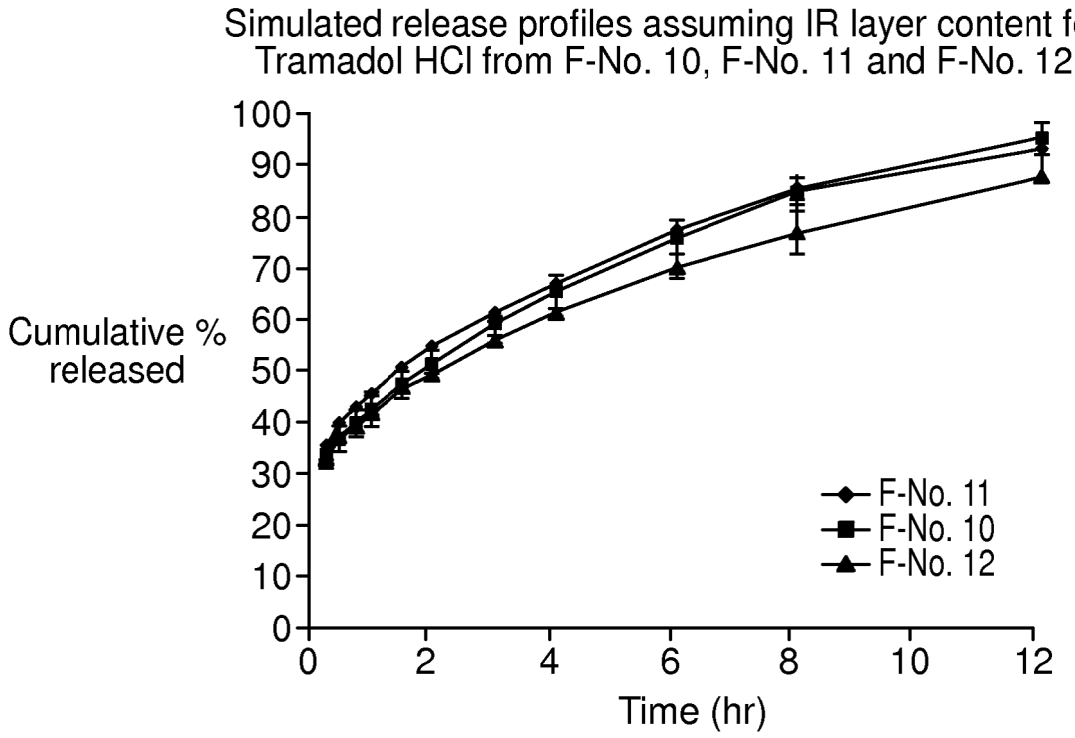

Simulated release profiles assuming IR layer content for Tramadol HCl from F-No. 10, F-No. 11 and F-No. 12
Cumulative % released
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
F-No. 11
F-No. 10
F-No. 12

FIG. 26

In vitro release profiles for Acetaminophen from F-No. 10

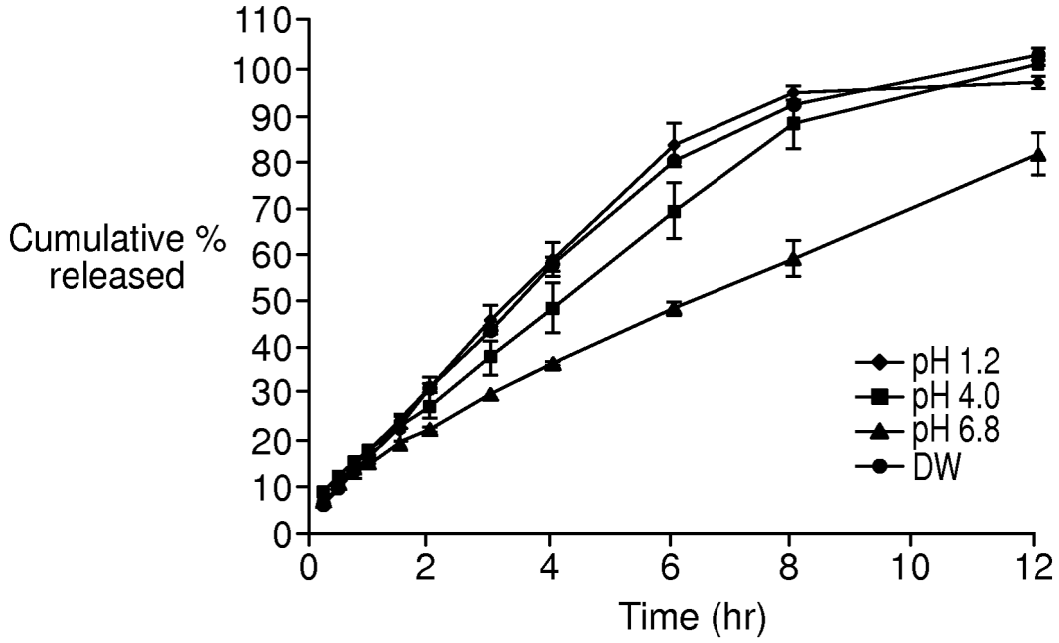


FIG. 27

In vitro release profiles for Tramadol HCl from F-No. 10

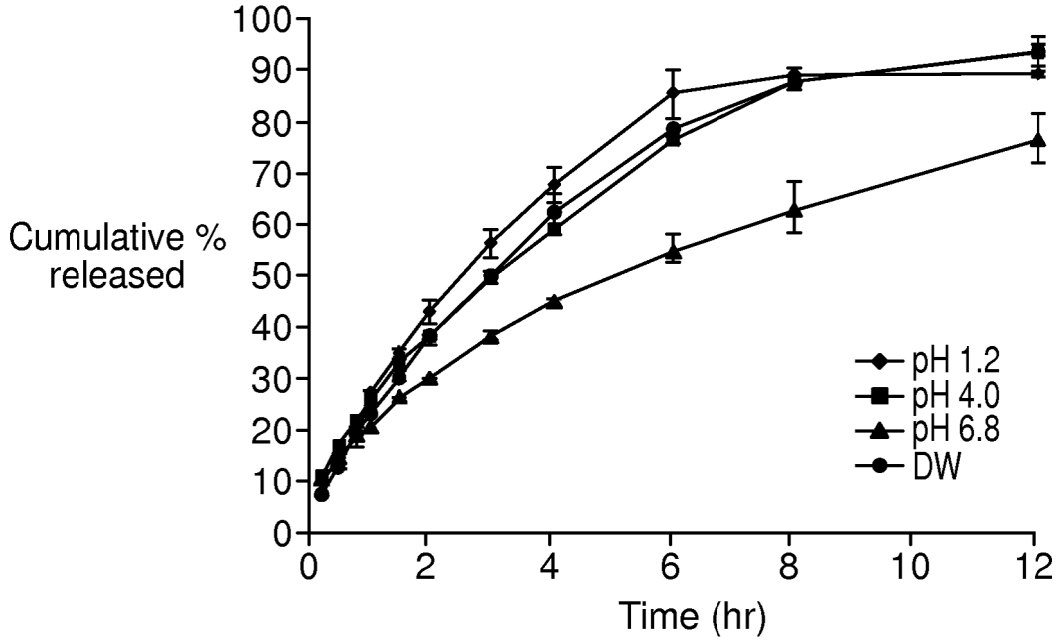


FIG. 28

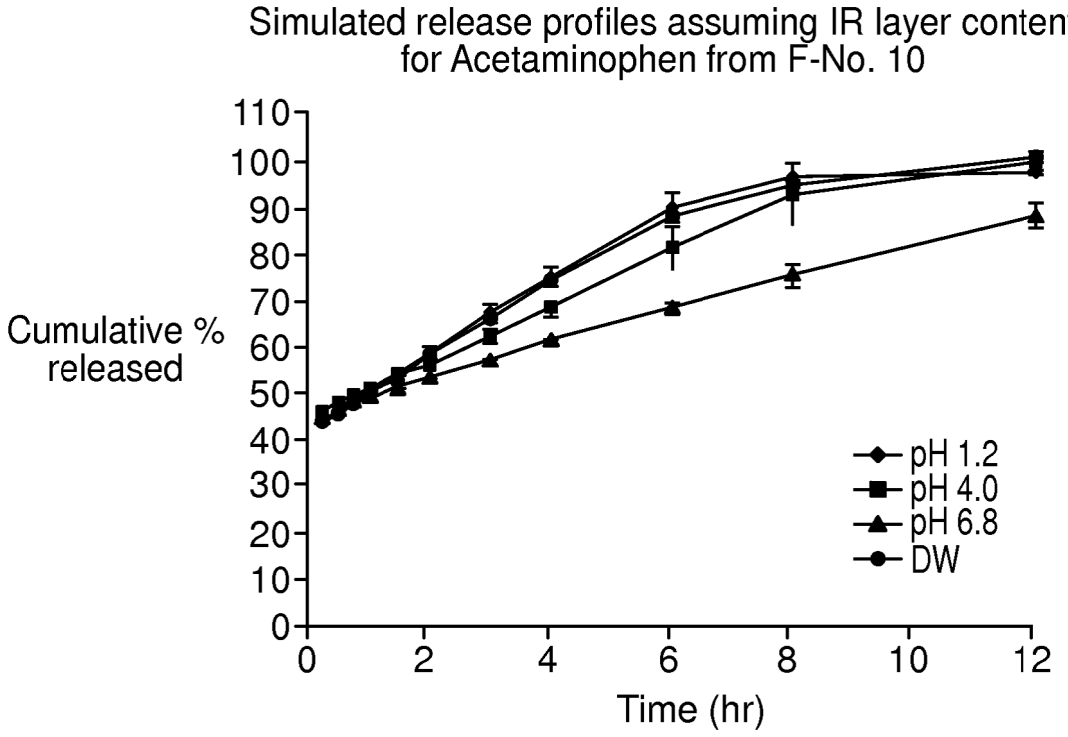

Simulated release profiles assuming IR layer content
for Acetaminophen from F-No. 10
Cumulative %
released
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
pH 1.2
pH 4.0
pH 6.8
DW

FIG. 29

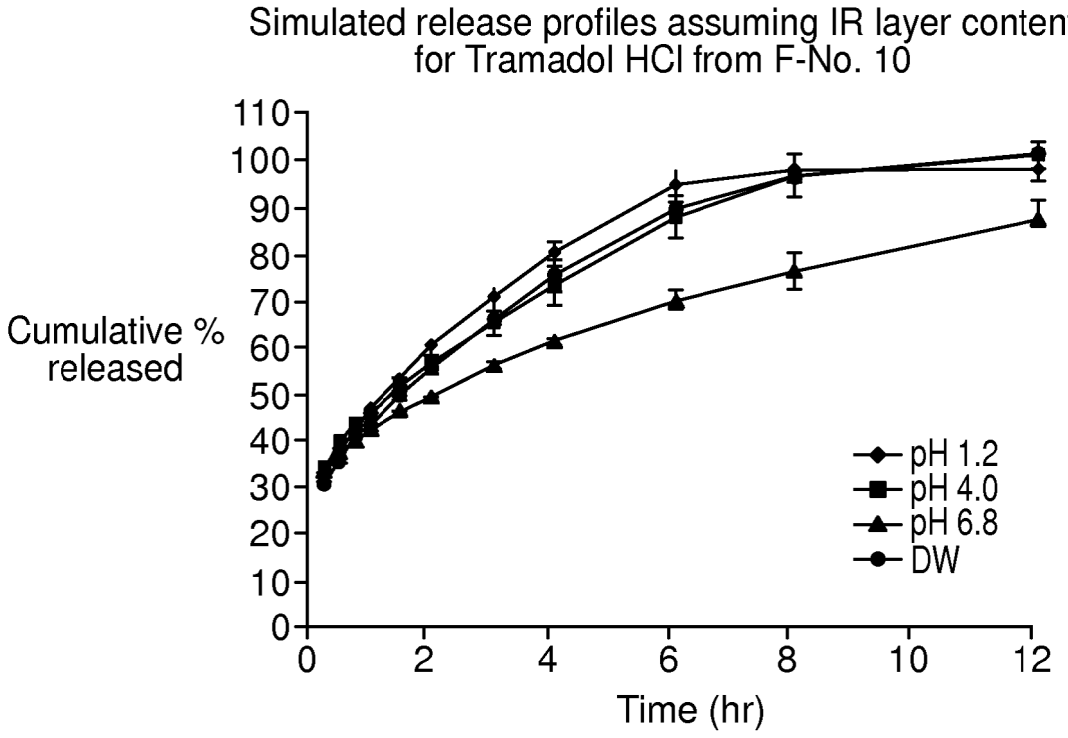

Simulated release profiles assuming IR layer content
for Tramadol HCl from F-No. 10
Cumulative %
released
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
pH 1.2
pH 4.0
pH 6.8
DW

FIG. 30

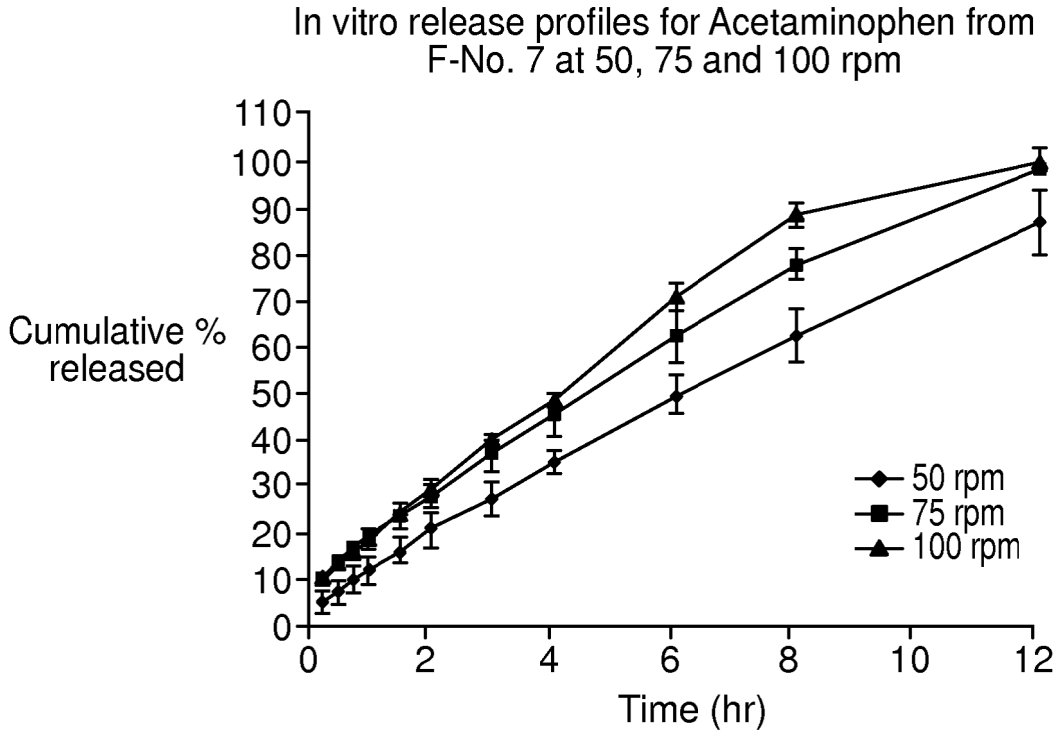

In vitro release profiles for Acetaminophen from F-No. 7 at 50, 75 and 100 rpm
Cumulative % released
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
50 rpm
75 rpm
100 rpm

FIG. 31

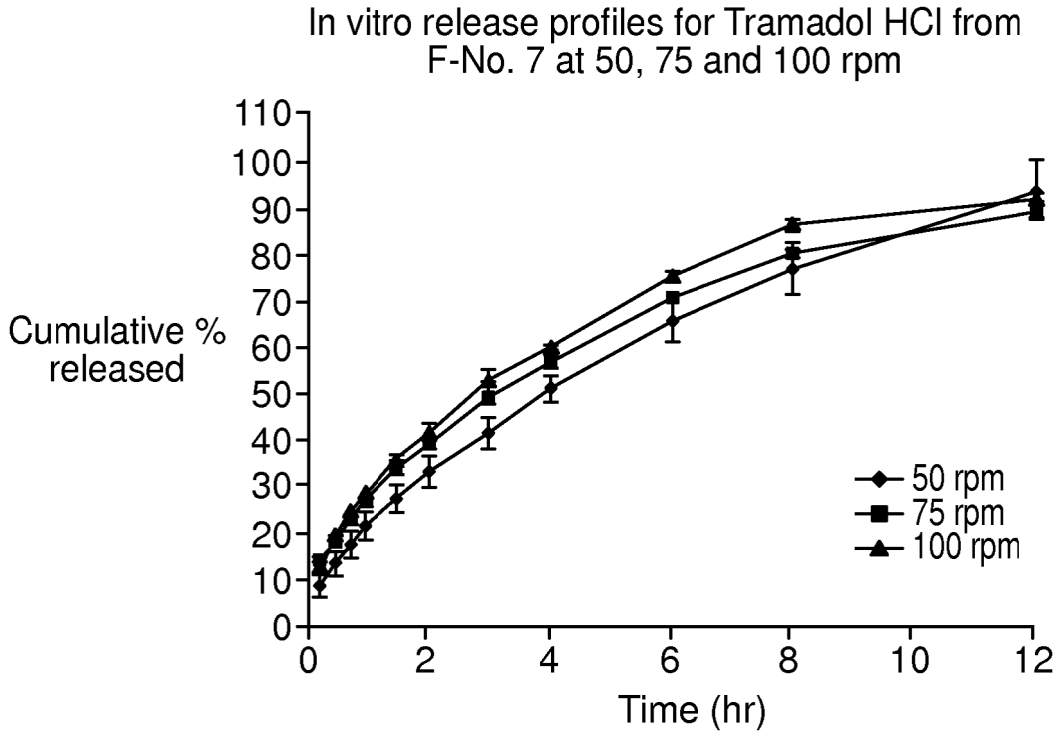

In vitro release profiles for Tramadol HCl from F-No. 7 at 50, 75 and 100 rpm
Cumulative % released
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
50 rpm
75 rpm
100 rpm

FIG. 32

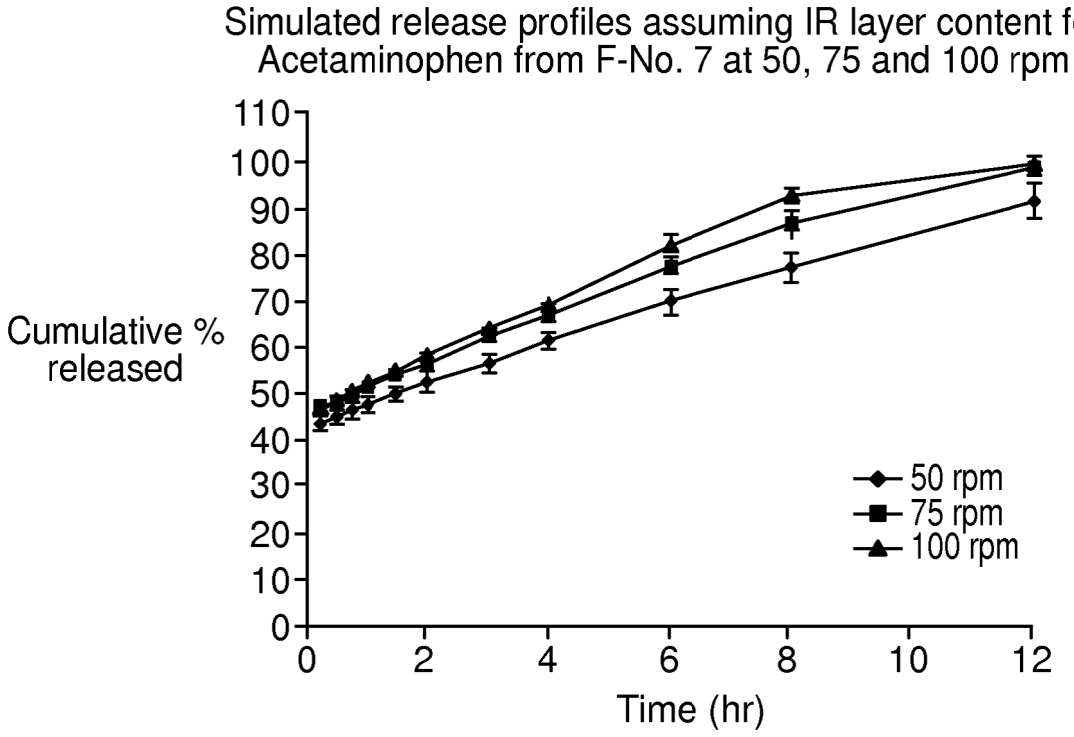

Simulated release profiles assuming IR layer content for Acetaminophen from F-No. 7 at 50, 75 and 100 rpm
Cumulative % released
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
50 rpm
75 rpm
100 rpm

FIG. 33

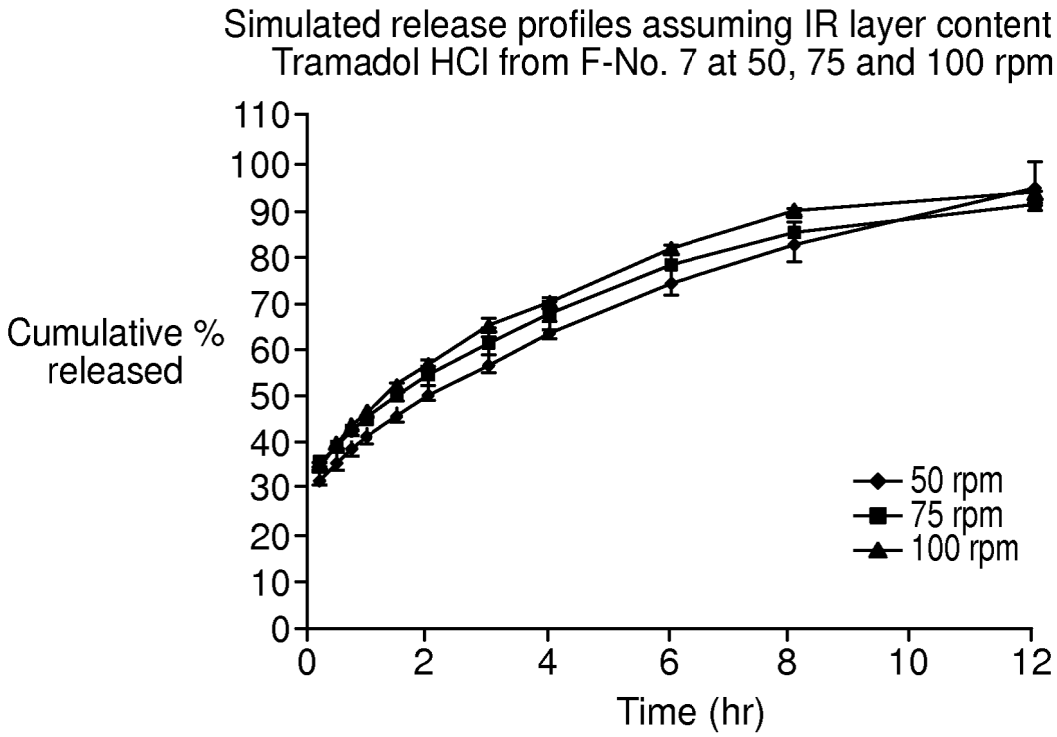

Simulated release profiles assuming IR layer content for Tramadol HCl from F-No. 7 at 50, 75 and 100 rpm
Cumulative % released
110
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (hr)
50 rpm
75 rpm
100 rpm

FIG. 34

In vitro release profiles for (a) Acetaminophen and (b) Tramadol HCl from F-No. 13 at 50 rpm in pH 1.2 buffer solution for first 2 hours and pH 6.8 buffer solution from 2 to 12 hours

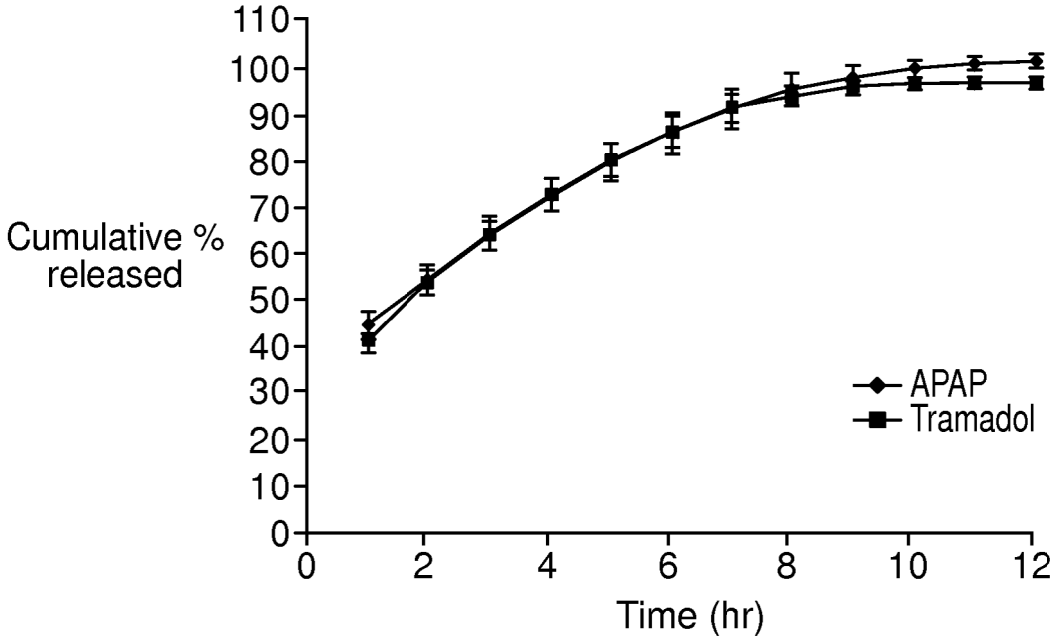


FIG. 35

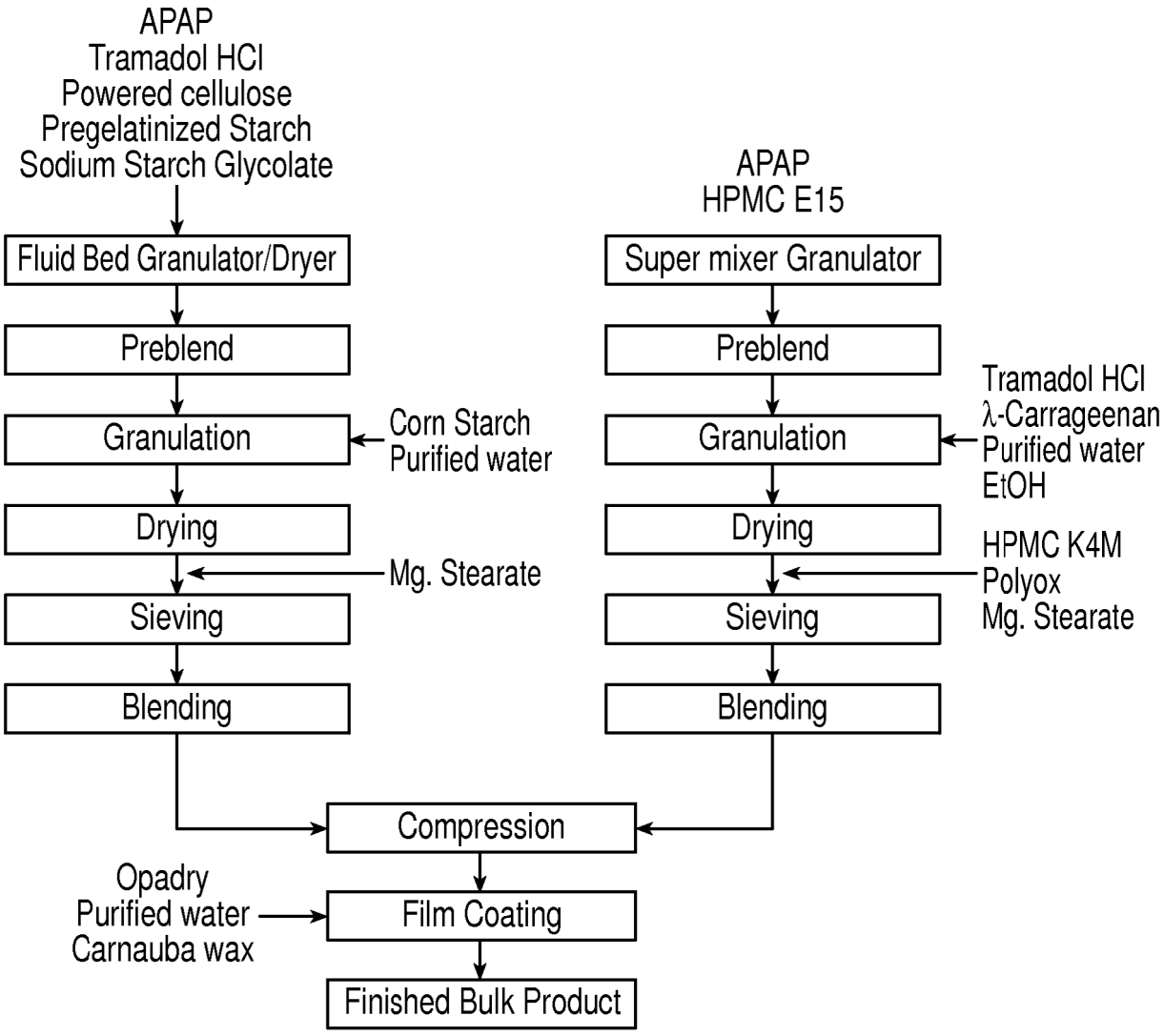

APAP
Tramadol HCl
Powered cellulose
Pregelatinized Starch
Sodium Starch Glycolate
Fluid Bed Granulator/Dryer
Preblend
Granulation
Corn Starch
Purified water
Drying
Mg. Stearate
Sieving
Blending
APAP
HPMC E15
Super mixer Granulator
Preblend
Granulation
Tramadol HCl
λ-Carrageenan
Purified water
EtOH
Drying
HPMC K4M
Polyox
Mg. Stearate
Sieving
Blending
Compression
Opadry
Purified water
Carnauba wax
Film Coating
Finished Bulk Product

FIG. 36

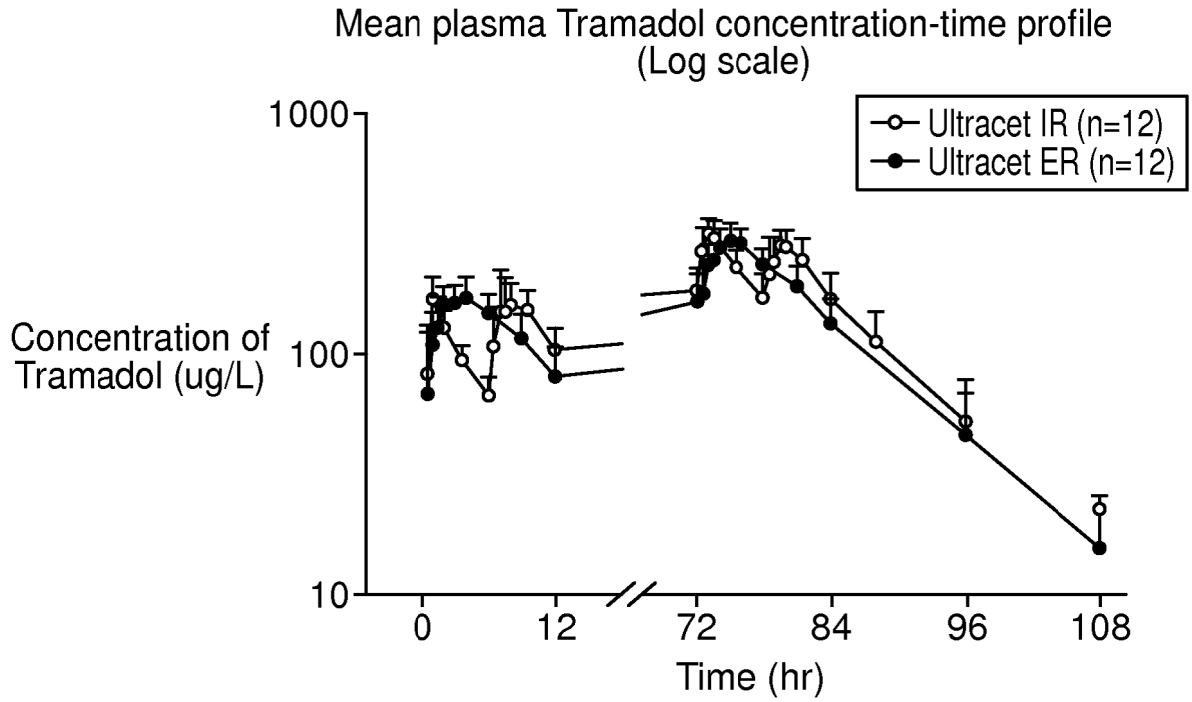
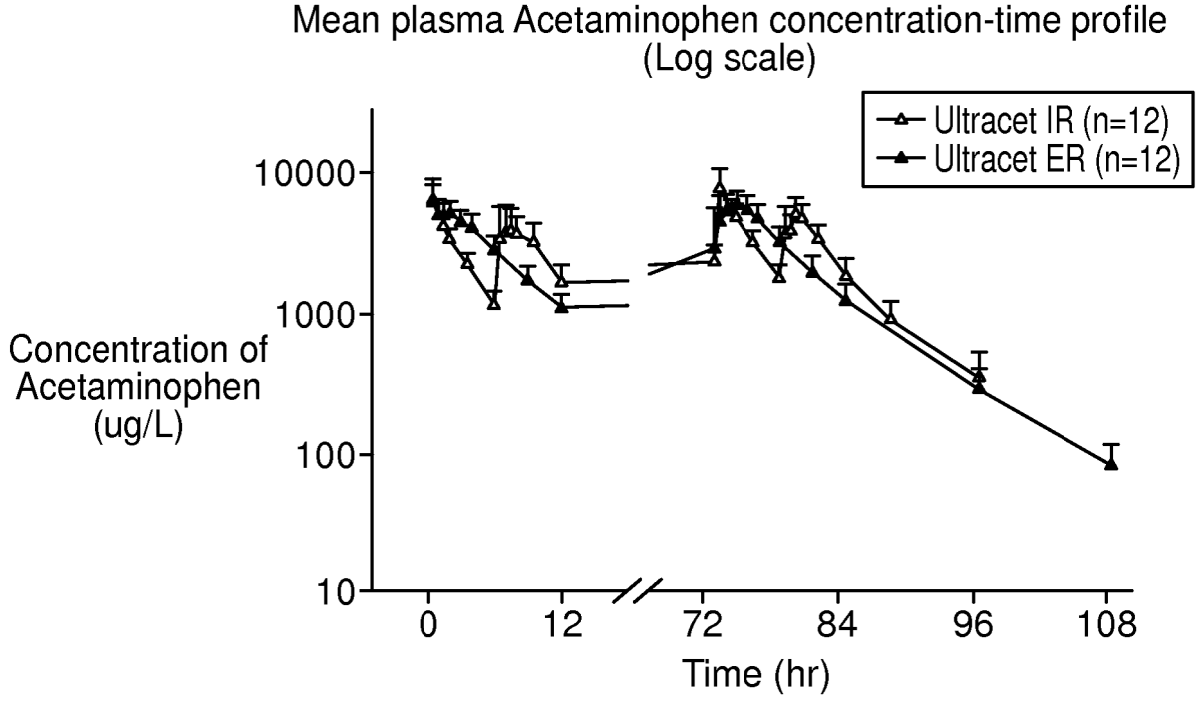

Mean plasma Tramadol concentration-time profile
(Log scale)
Ultracet IR (n=12)
Ultracet ER (n=12)
Concentration of Tramadol (ug/L)
1000
100
10
0
12
72
84
96
108
Time (hr)

FIG. 37


Mean plasma Acetaminophen concentration-time profile
(Log scale)
Ultracet IR (n=12)
Ultracet ER (n=12)
Concentration of Acetaminophen (ug/L)
10000
1000
100
10
0
12
72
84
96
108
Time (hr)