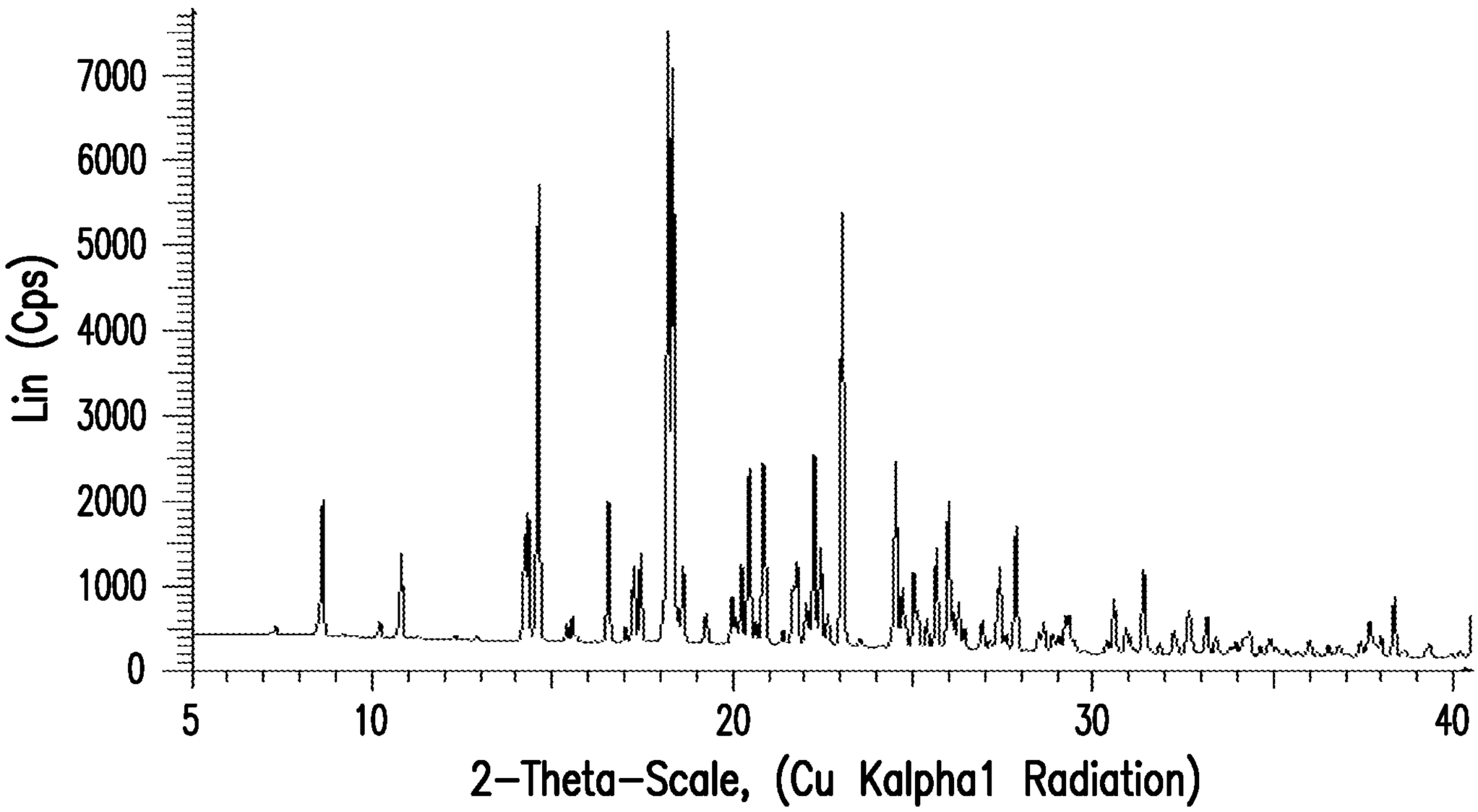

XRPD of Form K of a Free Base of Compound 1
Lin (Cps)
7000
6000
5000
4000
3000
2000
1000
0
5
10
20
30
40
2–Theta–Scale, (Cu Kalpha1 Radiation)

FIG. 1

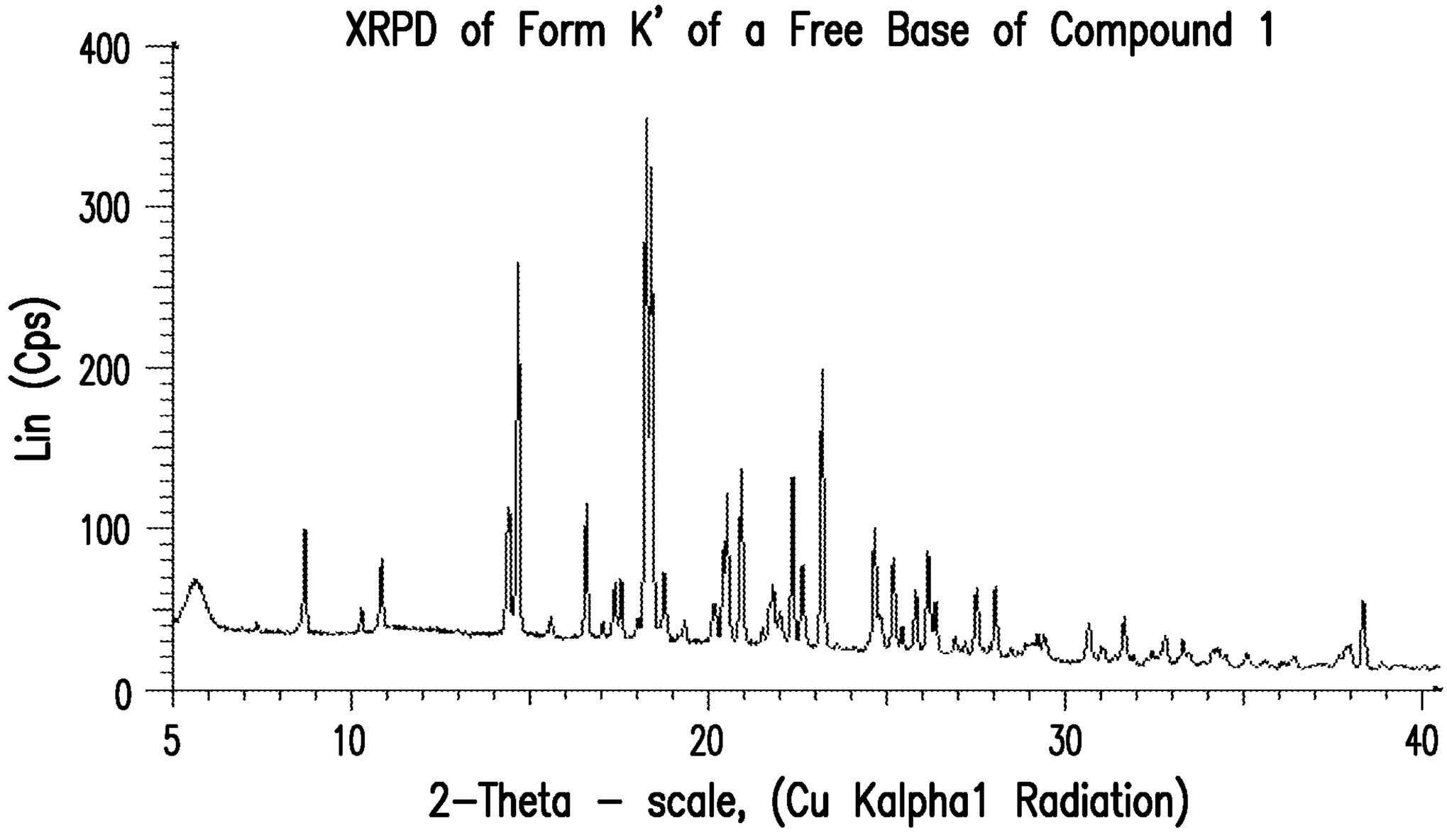

XRPD of Form K' of a Free Base of Compound 1
Lin (Cps)
400
300
200
100
0
5
10
20
30
40
2–Theta – scale, (Cu Kalpha1 Radiation)

FIG. 2

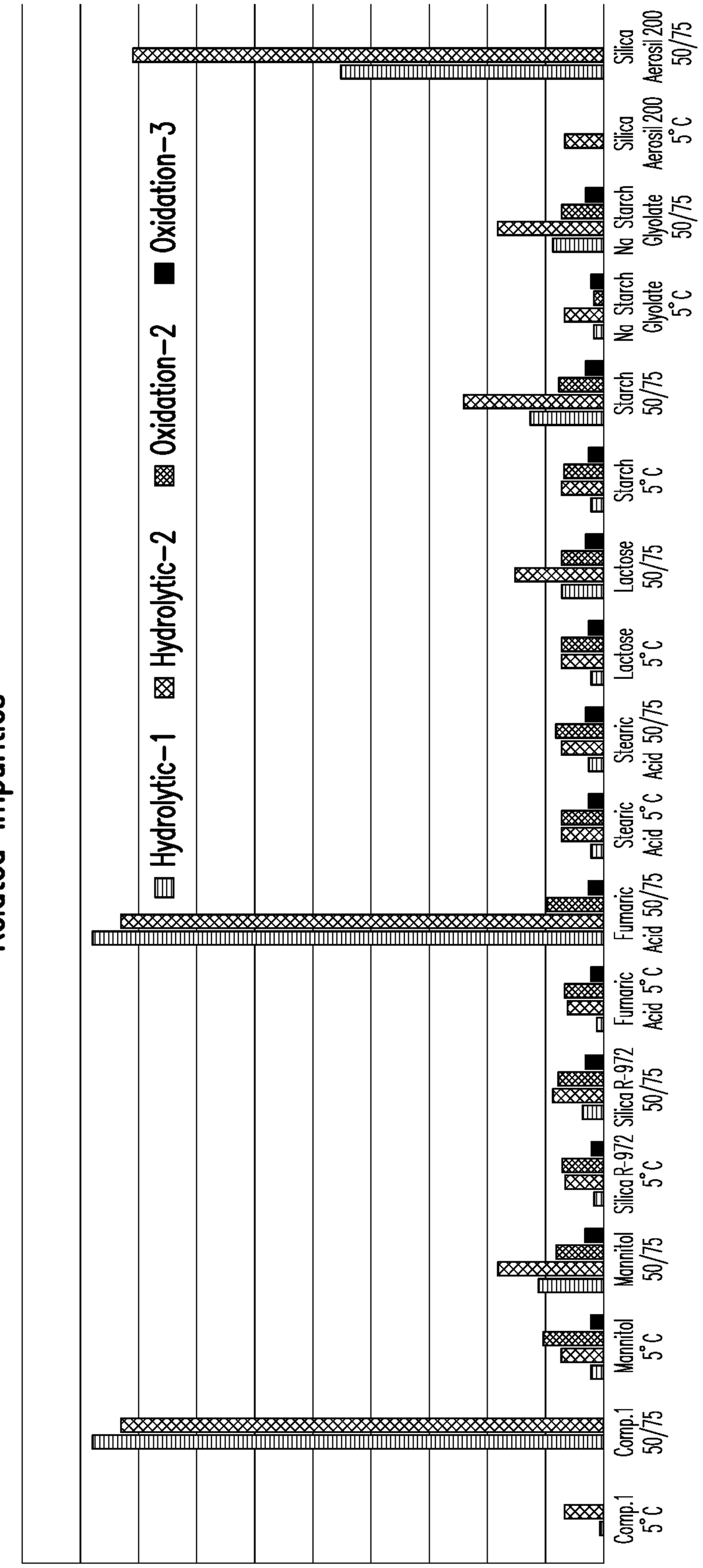

Related Impurities
% Chemical Degradation
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Hydrolytic–1
Hydrolytic–2
Oxidation–2
Oxidation–3
Comp.1 5°C
Comp.1 50/75
Mannitol 5°C
Mannitol 50/75
Silica R-972 5°C
Silica R-972 50/75
Fumaric Acid 5°C
Fumaric Acid 50/75
Stearic Acid 5°C
Stearic Acid 50/75
Lactose 5°C
Lactose 50/75
Starch 5°C
Starch 50/75
No Starch Glyolate 5°C
No Starch Glyolate 50/75
Silica Aerosil 200 5°C
Silica Aerosil 200 50/75

FIG. 3

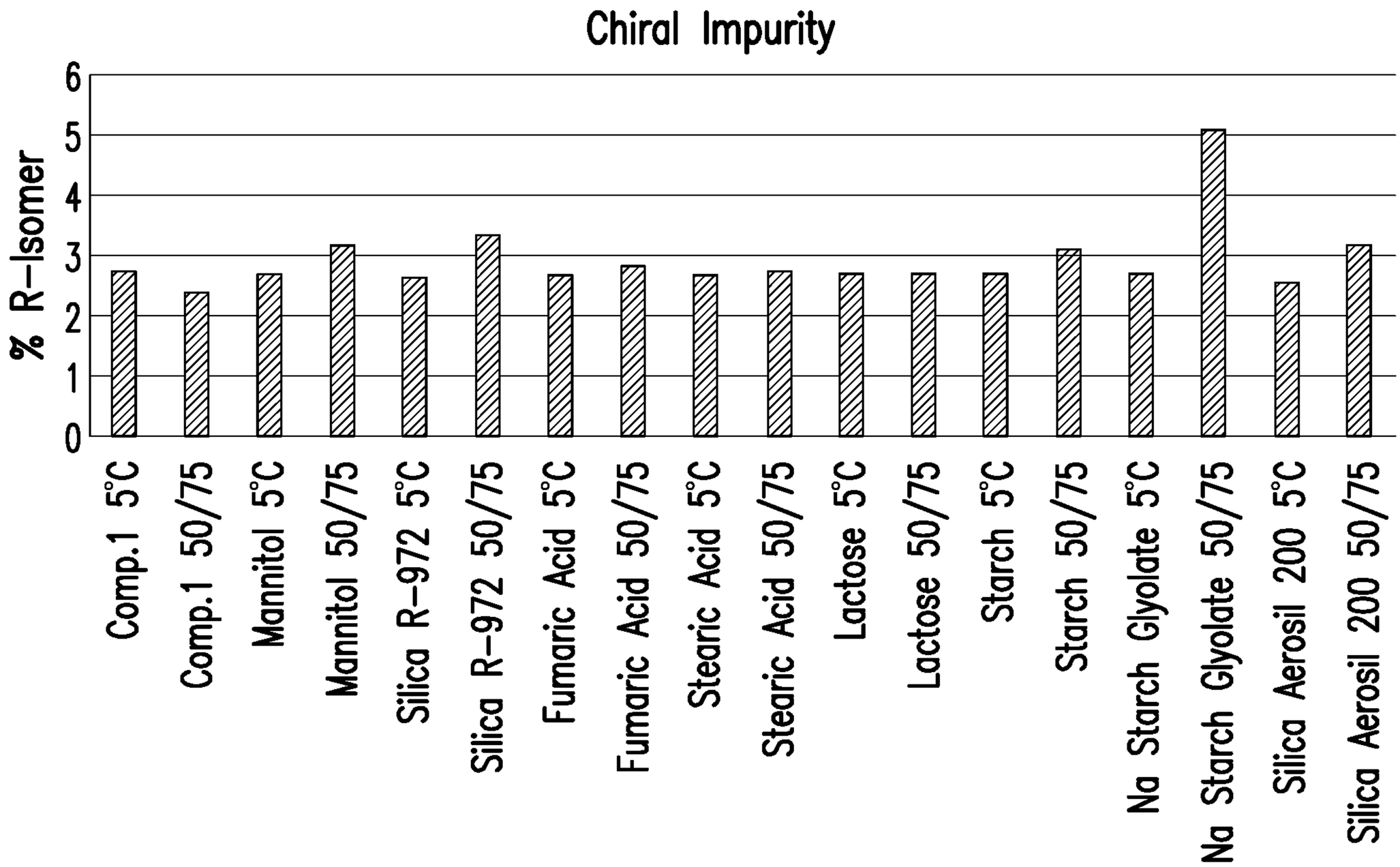

Chiral Impurity
% R-Isomer
6
5
4
3
2
1
0
Comp.1 5°C
Comp.1 50/75
Mannitol 5°C
Mannitol 50/75
Silica R-972 5°C
Silica R-972 50/75
Fumaric Acid 5°C
Fumaric Acid 50/75
Stearic Acid 5°C
Stearic Acid 50/75
Lactose 5°C
Lactose 50/75
Starch 5°C
Starch 50/75
Na Starch Glyolate 5°C
Na Starch Glyolate 50/75
Silica Aerosil 200 5°C
Silica Aerosil 200 50/75

FIG. 4

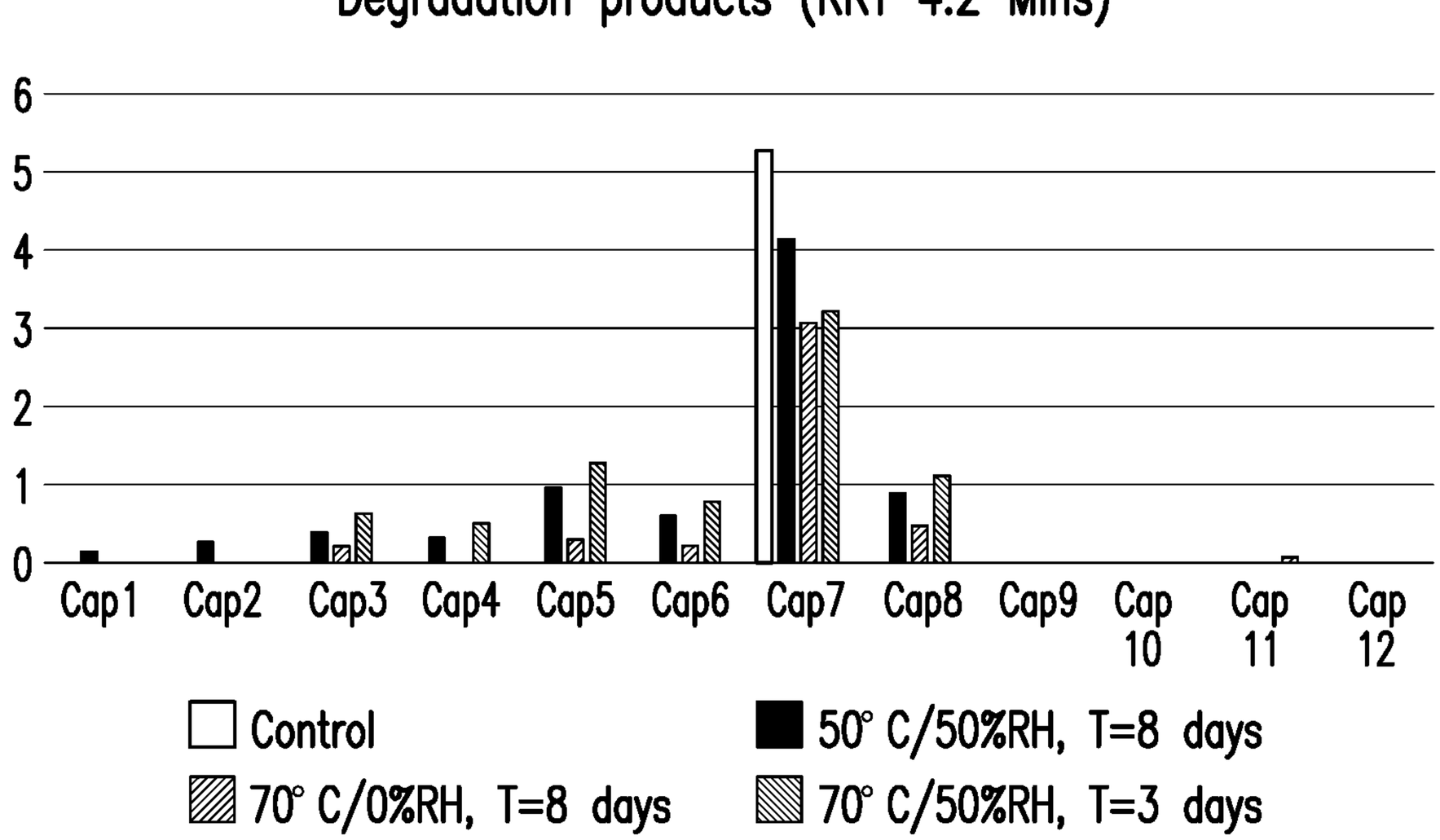

Degradation products (RRT 4.2 Mins)
6
5
4
3
2
1
0
Cap1
Cap2
Cap3
Cap4
Cap5
Cap6
Cap7
Cap8
Cap9
Cap 10
Cap 11
Cap 12
Control
50° C/50%RH, T=8 days
70° C/0%RH, T=8 days
70° C/50%RH, T=3 days

FIG. 5A

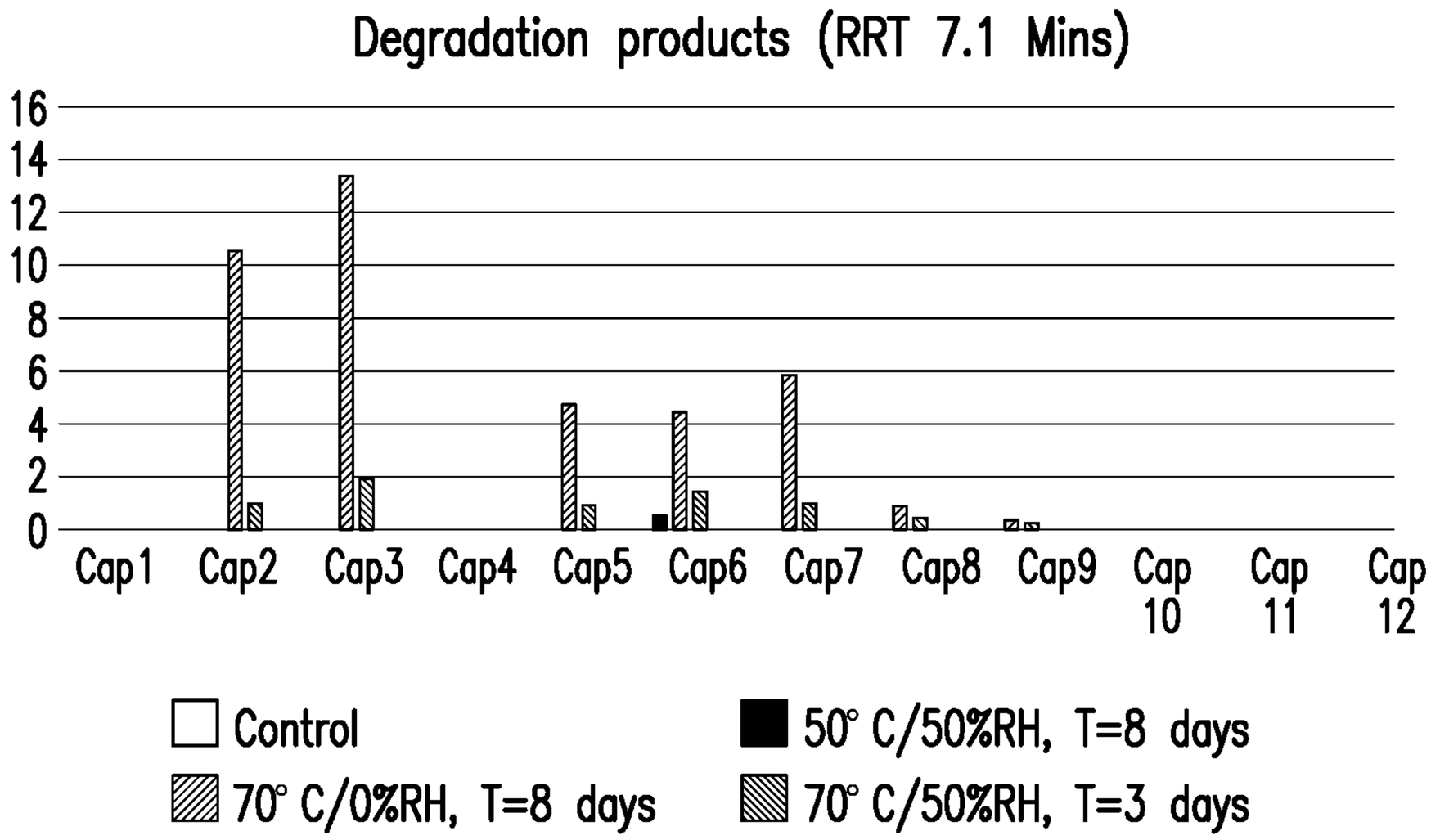

Degradation products (RRT 7.1 Mins)
16
14
12
10
8
6
4
2
0
Cap1
Cap2
Cap3
Cap4
Cap5
Cap6
Cap7
Cap8
Cap9
Cap 10
Cap 11
Cap 12
Control
50° C/50%RH, T=8 days
70° C/0%RH, T=8 days
70° C/50%RH, T=3 days

FIG. 5B

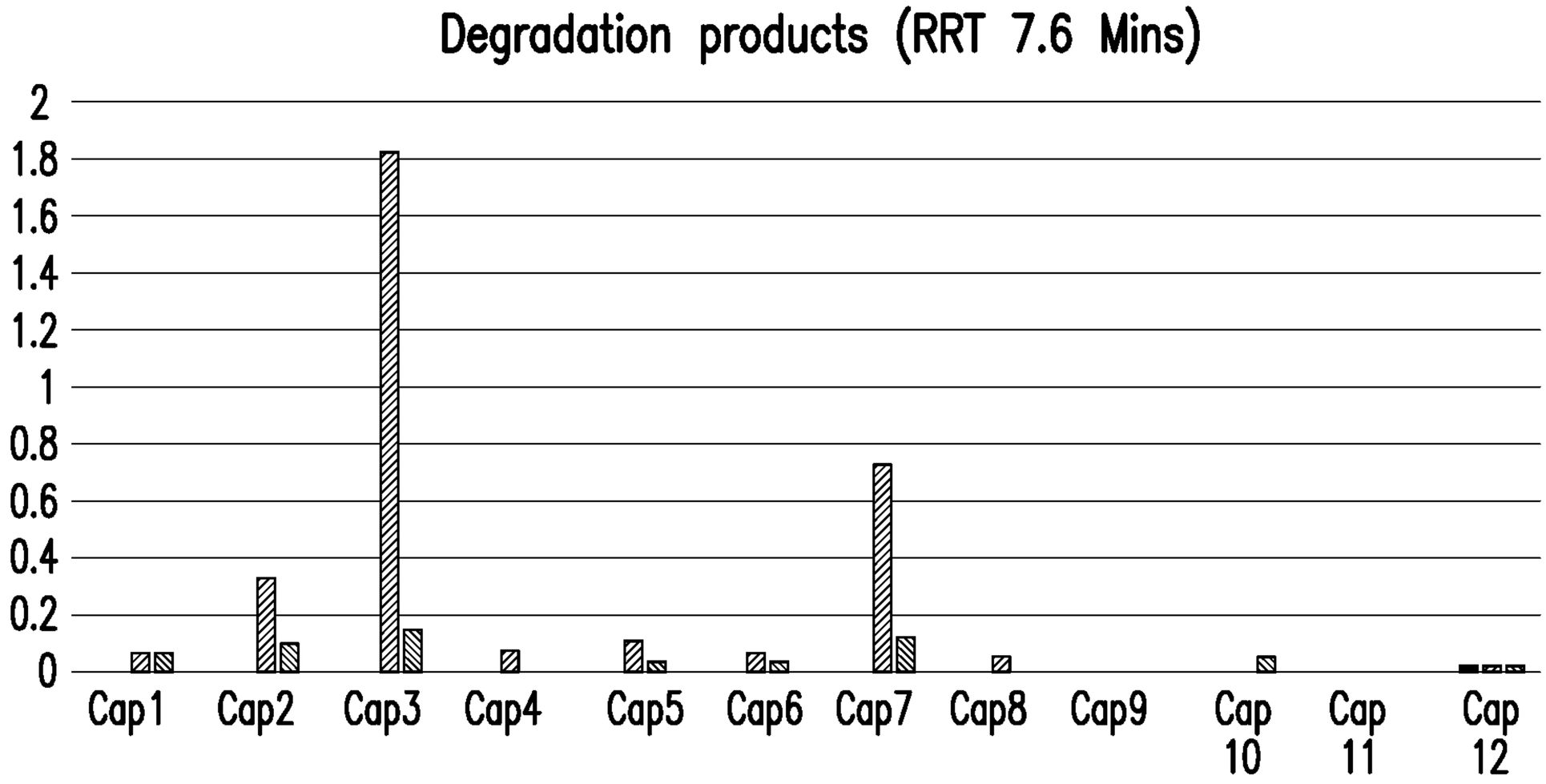

Degradation products (RRT 7.6 Mins)
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Cap1
Cap2
Cap3
Cap4
Cap5
Cap6
Cap7
Cap8
Cap9
Cap 10
Cap 11
Cap 12
Control
70° C/0%RH, T=8 days
50° C/50%RH, T=8 days
70° C/50%RH, T=3 days

FIG. 5C

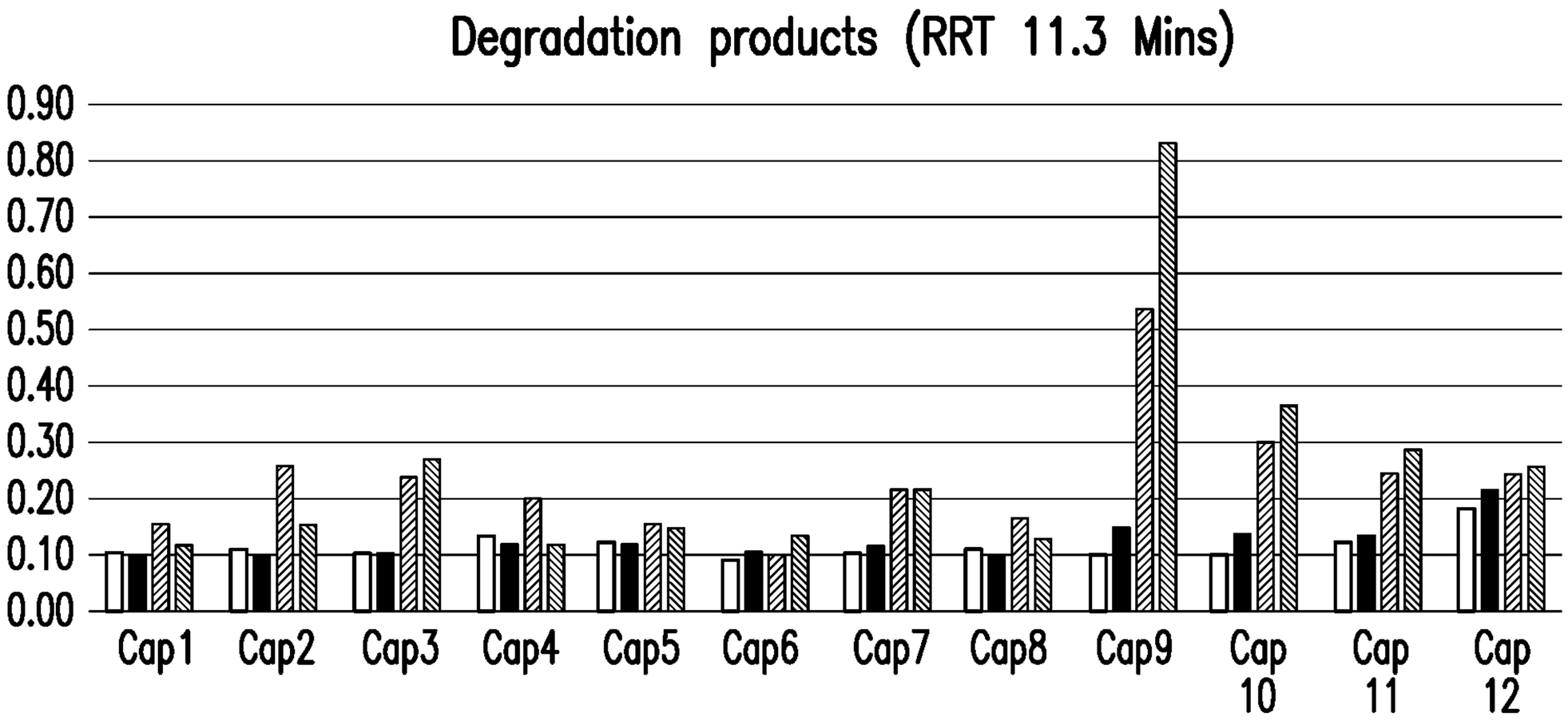

Degradation products (RRT 11.3 Mins)
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
Cap1
Cap2
Cap3
Cap4
Cap5
Cap6
Cap7
Cap8
Cap9
Cap 10
Cap 11
Cap 12
Control
70° C/0%RH, T=8 days
50° C/50%RH, T=8 days
70° C/50%RH, T=3 days

FIG. 5D

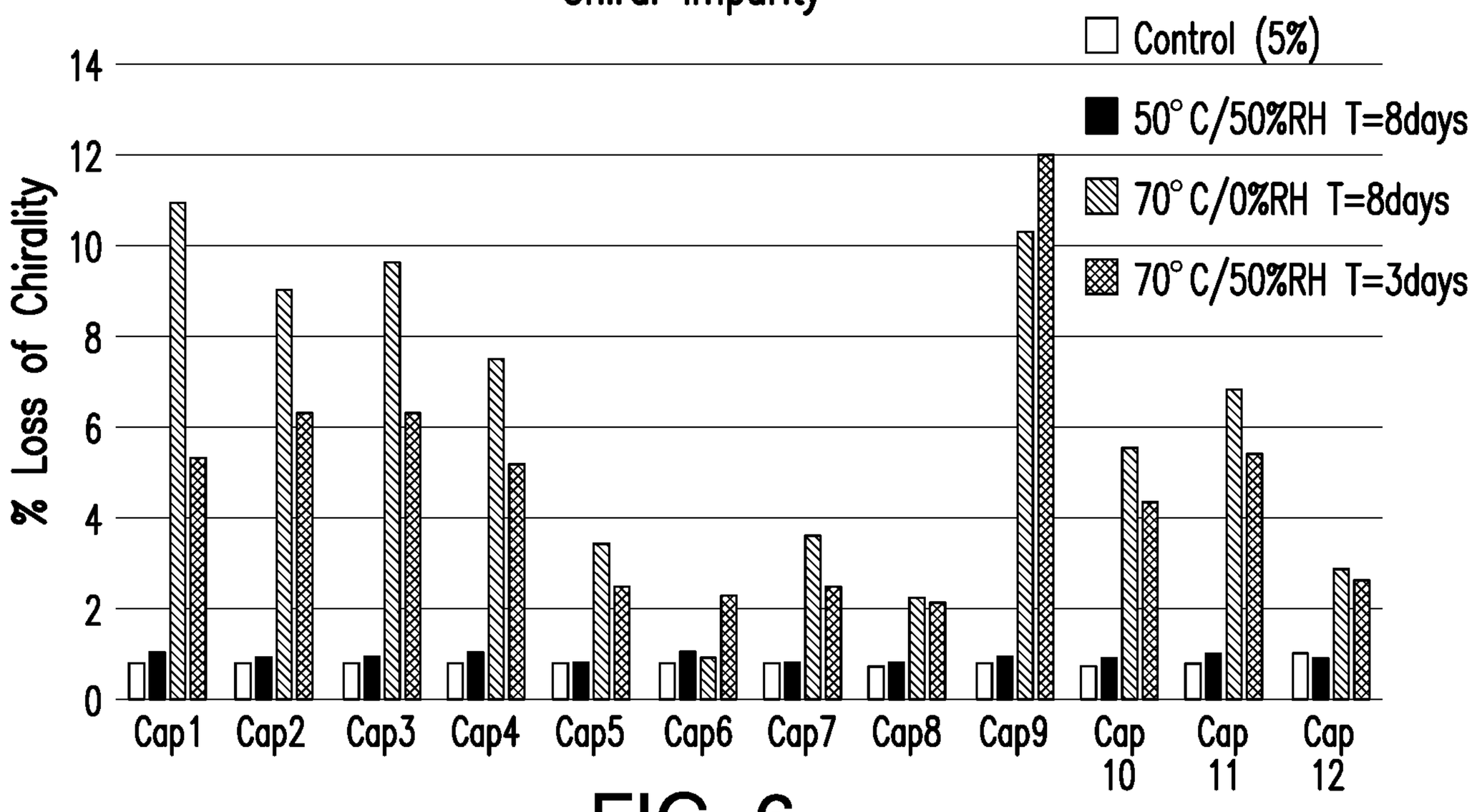

Chiral Impurity
% Loss of Chirality
0
2
4
6
8
10
12
14
Cap1
Cap2
Cap3
Cap4
Cap5
Cap6
Cap7
Cap8
Cap9
Cap 10
Cap 11
Cap 12
Control (5%)
50° C/50%RH T=8days
70° C/0%RH T=8days
70° C/50%RH T=3days

FIG. 6

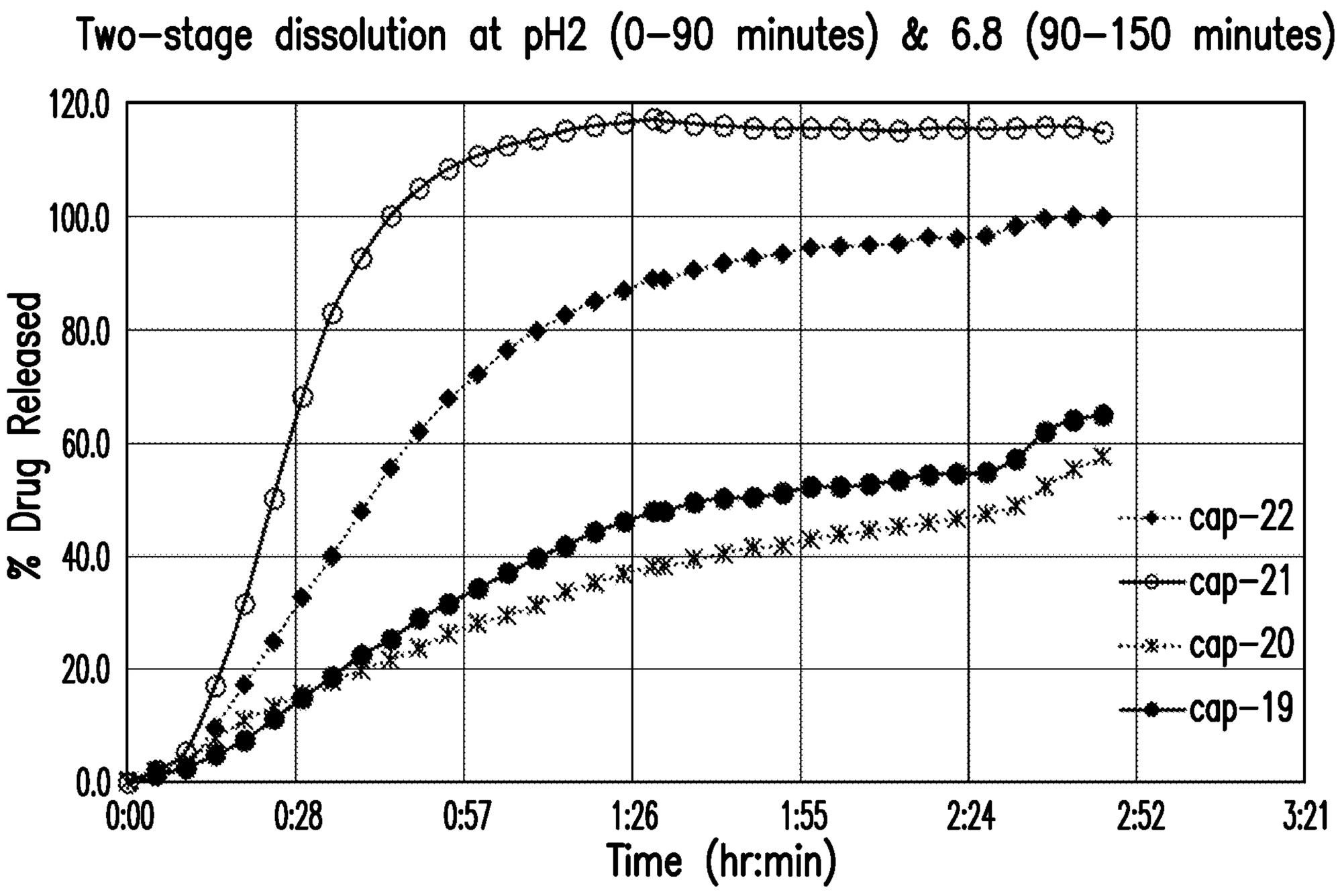

Two-stage dissolution at pH2 (0-90 minutes) & 6.8 (90-150 minutes)
% Drug Released
0.0
20.0
40.0
60.0
80.0
100.0
120.0
0:00
0:28
0:57
1:26
1:55
2:24
2:52
3:21
Time (hr:min)
cap-22
cap-21
cap-20
cap-19

FIG. 7

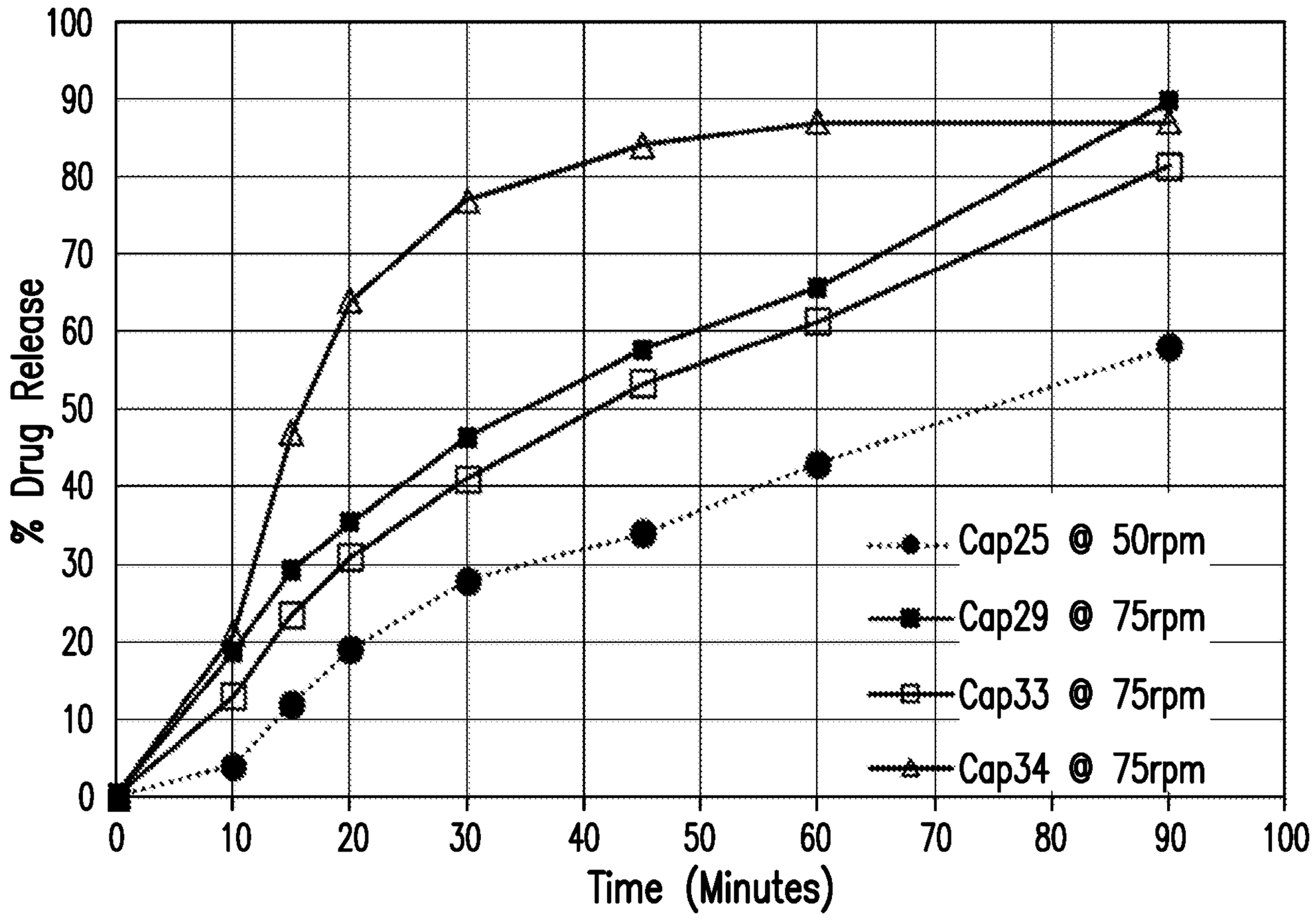

Comparative dissolution release profiles
% Drug Release
Time (Minutes)
0
10
20
30
40
50
60
70
80
90
100
Cap25 @ 50rpm
Cap29 @ 75rpm
Cap33 @ 75rpm
Cap34 @ 75rpm

FIG. 8

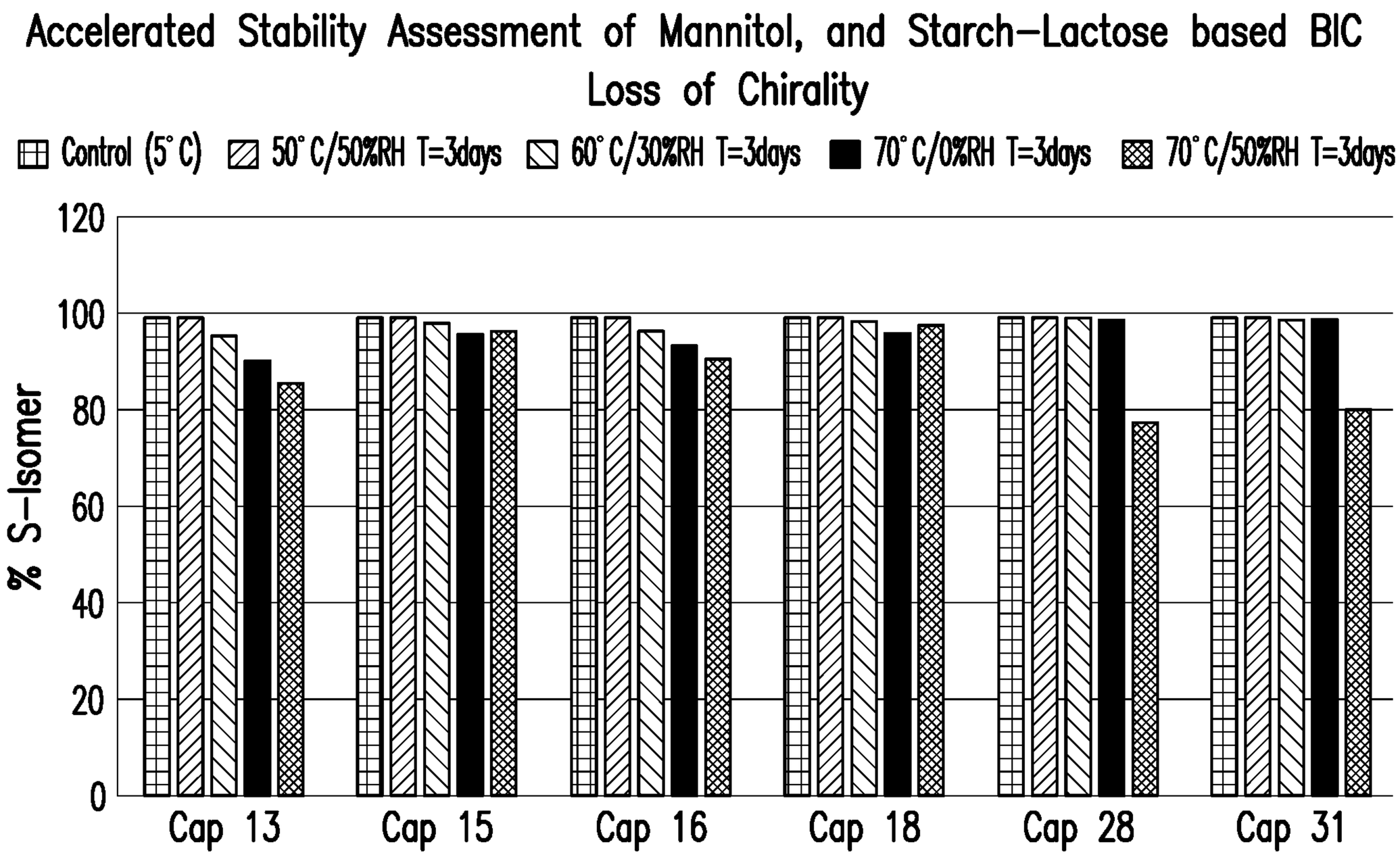

Accelerated Stability Assessment of Mannitol, and Starch–Lactose based BIC
Loss of Chirality
Control (5° C)
50° C/50%RH T=3days
60° C/30%RH T=3days
70° C/0%RH T=3days
70° C/50%RH T=3days
% S–Isomer
0
20
40
60
80
100
120
Cap 13
Cap 15
Cap 16
Cap 18
Cap 28
Cap 31

FIG. 9

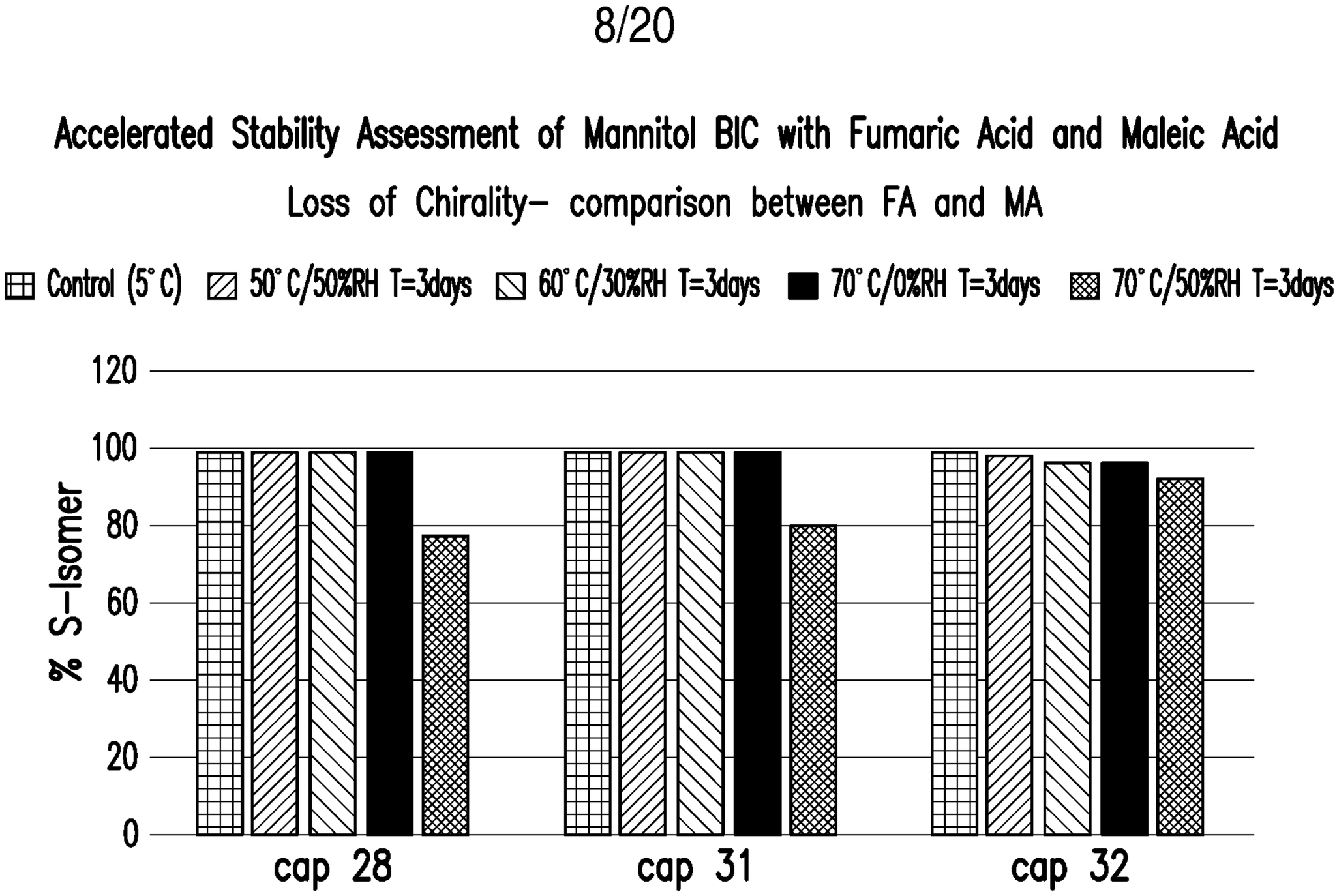

Accelerated Stability Assessment of Mannitol BIC with Fumaric Acid and Maleic Acid
Loss of Chirality– comparison between FA and MA
Control (5° C)
50° C/50%RH T=3days
60° C/30%RH T=3days
70° C/0%RH T=3days
70° C/50%RH T=3days
% S–Isomer
120
100
80
60
40
20
0
cap 28
cap 31
cap 32

FIG. 10

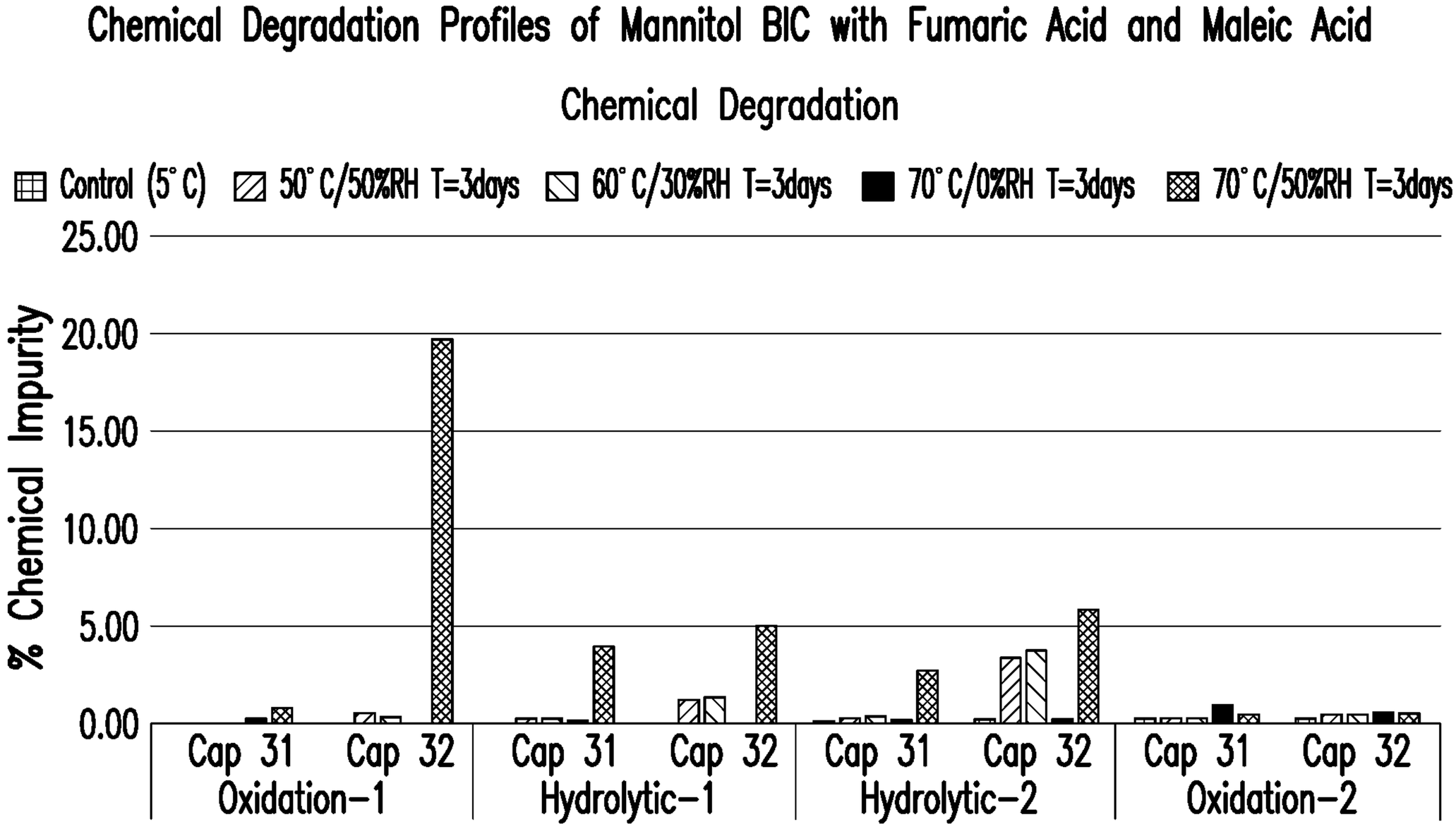

Chemical Degradation Profiles of Mannitol BIC with Fumaric Acid and Maleic Acid
Chemical Degradation
Control (5° C)
50° C/50%RH T=3days
60° C/30%RH T=3days
70° C/0%RH T=3days
70° C/50%RH T=3days
% Chemical Impurity
25.00
20.00
15.00
10.00
5.00
0.00
Cap 31
Cap 32
Oxidation–1
Hydrolytic–1
Hydrolytic–2
Oxidation–2

FIG. 11

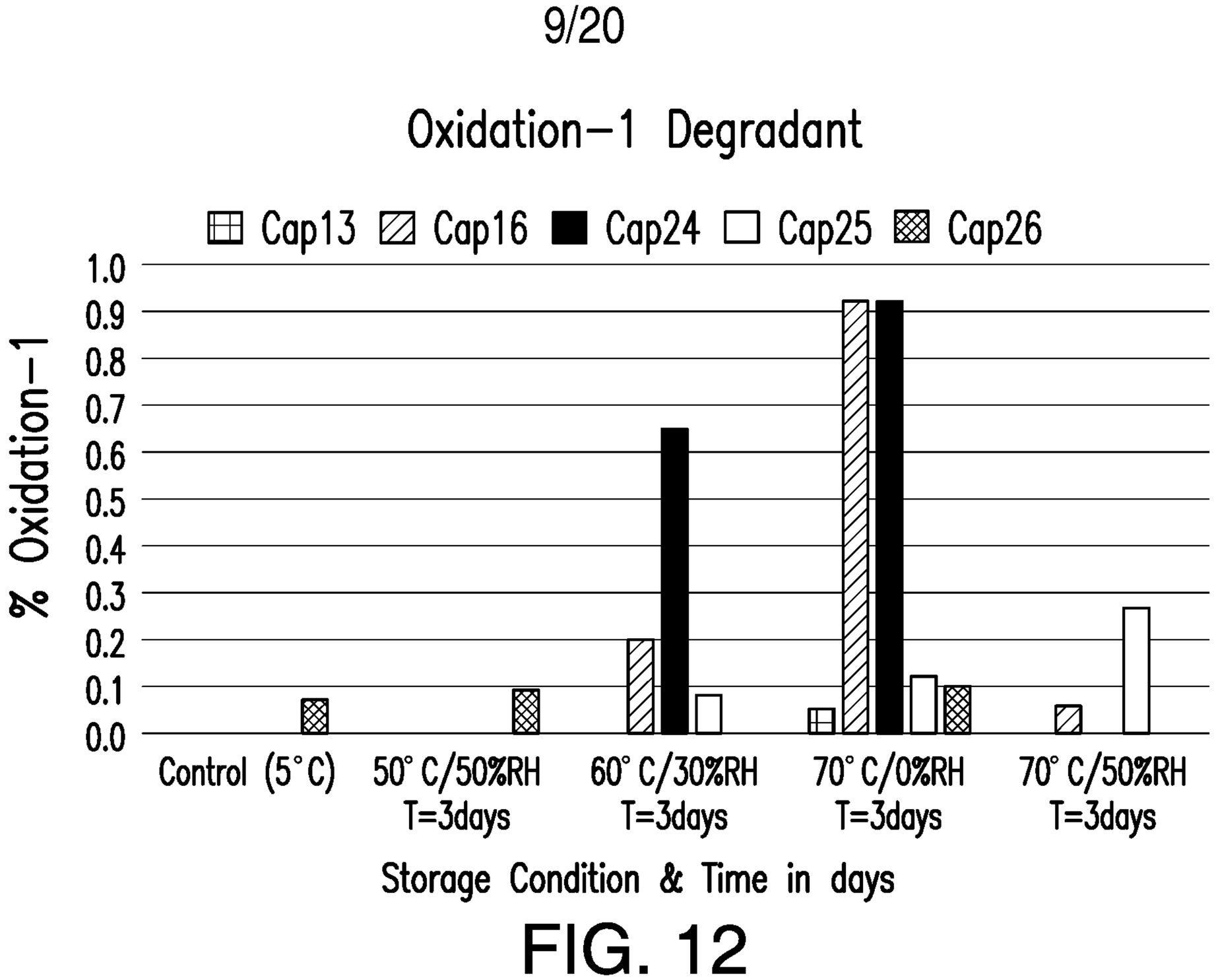

Oxidation–1 Degradant
Cap13 Cap16 Cap24 Cap25 Cap26
% Oxidation–1
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Control (5° C)
50° C/50%RH T=3days
60° C/30%RH T=3days
70° C/0%RH T=3days
70° C/50%RH T=3days
Storage Condition & Time in days

FIG. 12

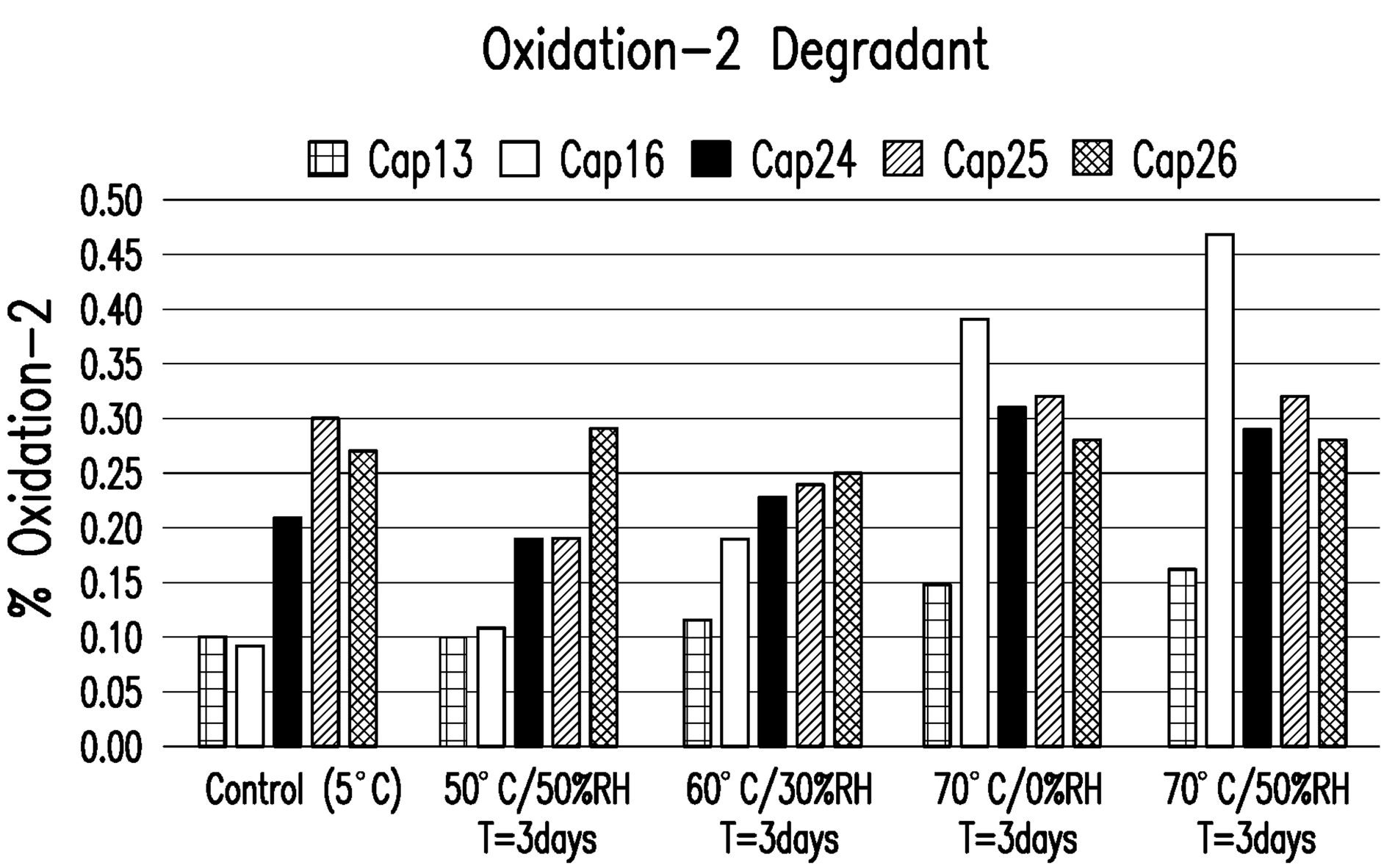

Oxidation–2 Degradant
Cap13 Cap16 Cap24 Cap25 Cap26
% Oxidation–2
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
Control (5° C)
50° C/50%RH T=3days
60° C/30%RH T=3days
70° C/0%RH T=3days
70° C/50%RH T=3days
Storage Condition & Time in days

FIG. 13

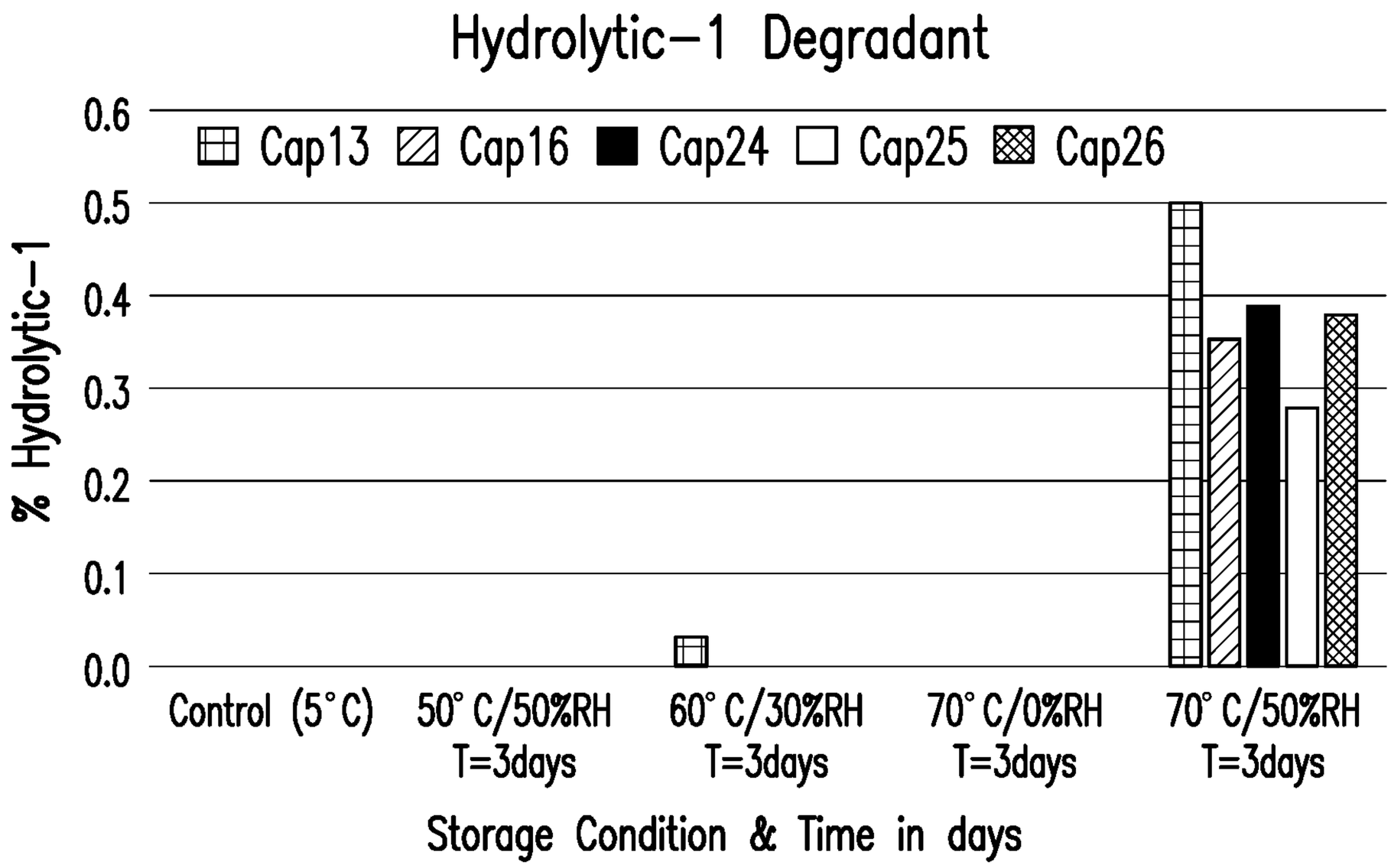

Hydrolytic–1 Degradant
0.6
0.5
0.4
0.3
0.2
0.1
0.0
% Hydrolytic–1
Cap13 Cap16 Cap24 Cap25 Cap26
Control (5° C)
50° C/50%RH T=3days
60° C/30%RH T=3days
70° C/0%RH T=3days
70° C/50%RH T=3days
Storage Condition & Time in days

FIG. 14

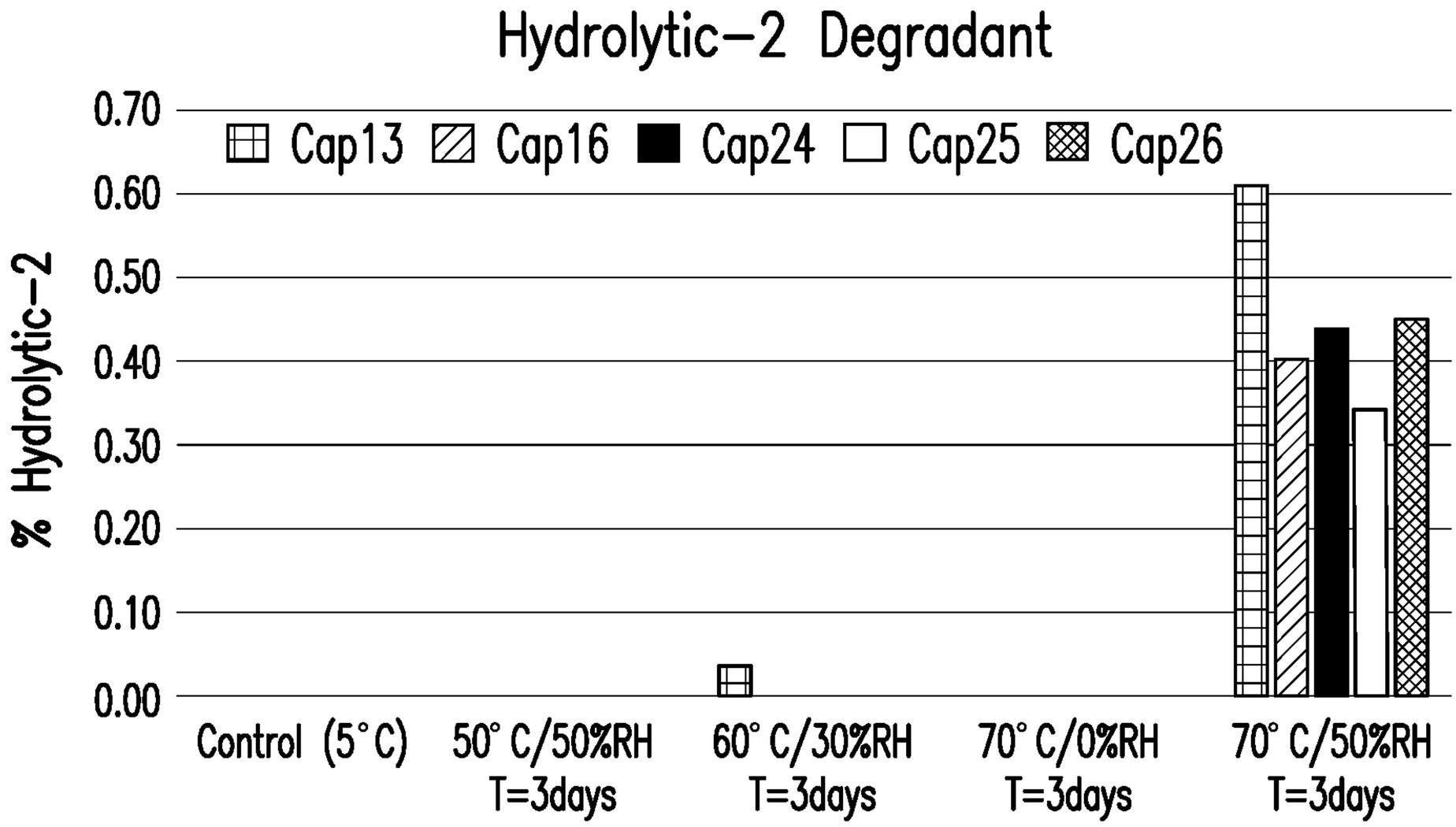

Hydrolytic–2 Degradant
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
% Hydrolytic–2
Cap13 Cap16 Cap24 Cap25 Cap26
Control (5° C)
50° C/50%RH T=3days
60° C/30%RH T=3days
70° C/0%RH T=3days
70° C/50%RH T=3days
Storage Condition & Time in days

FIG. 15

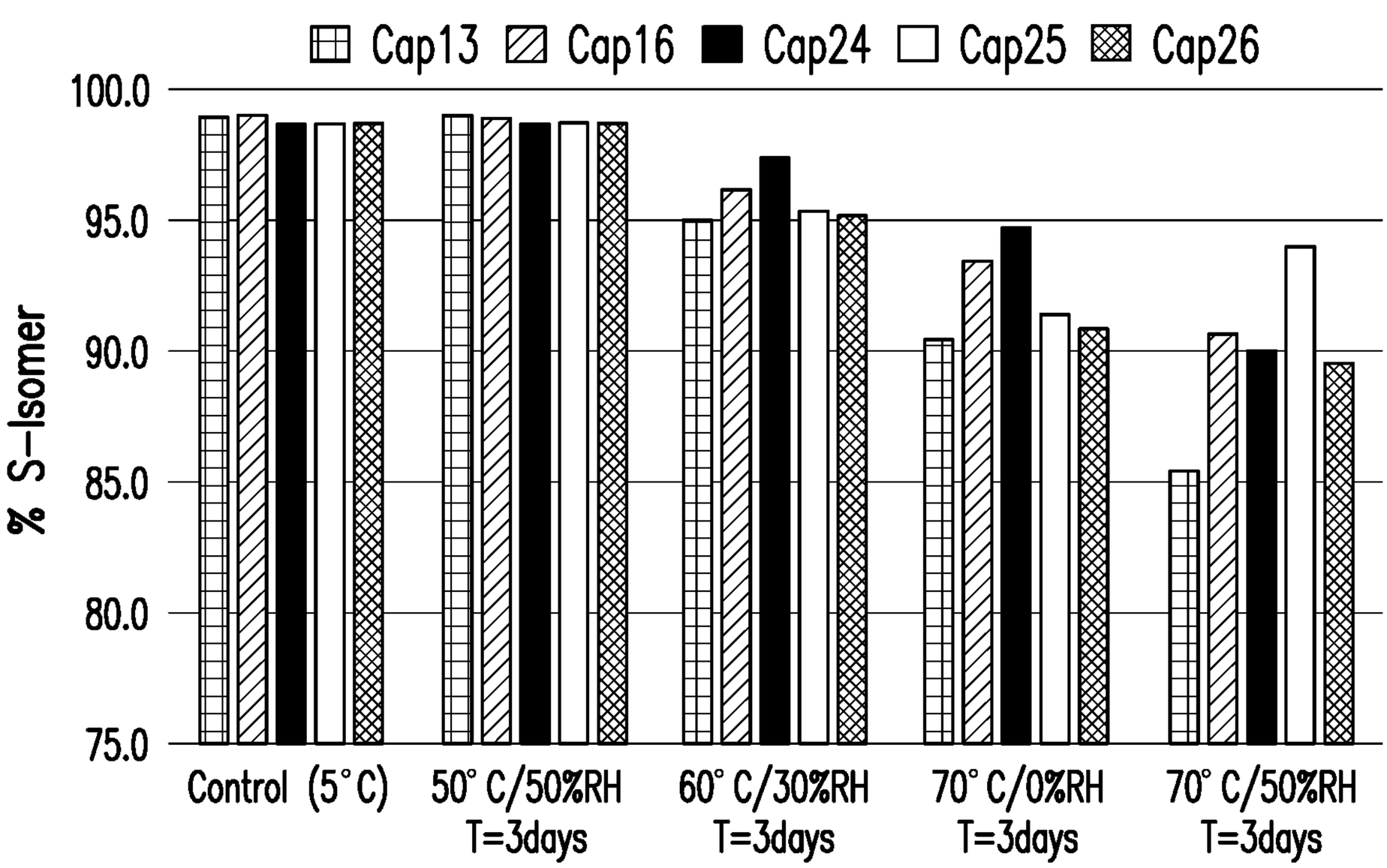

Loss of Chirality
Cap13
Cap16
Cap24
Cap25
Cap26
100.0
95.0
90.0
85.0
80.0
75.0
% S-Isomer
Control (5°C)
50° C/50%RH T=3days
60° C/30%RH T=3days
70° C/0%RH T=3days
70° C/50%RH T=3days
Storage Condition & Time in days

FIG. 16

Compound 1 Crystal without Aerosil R-972

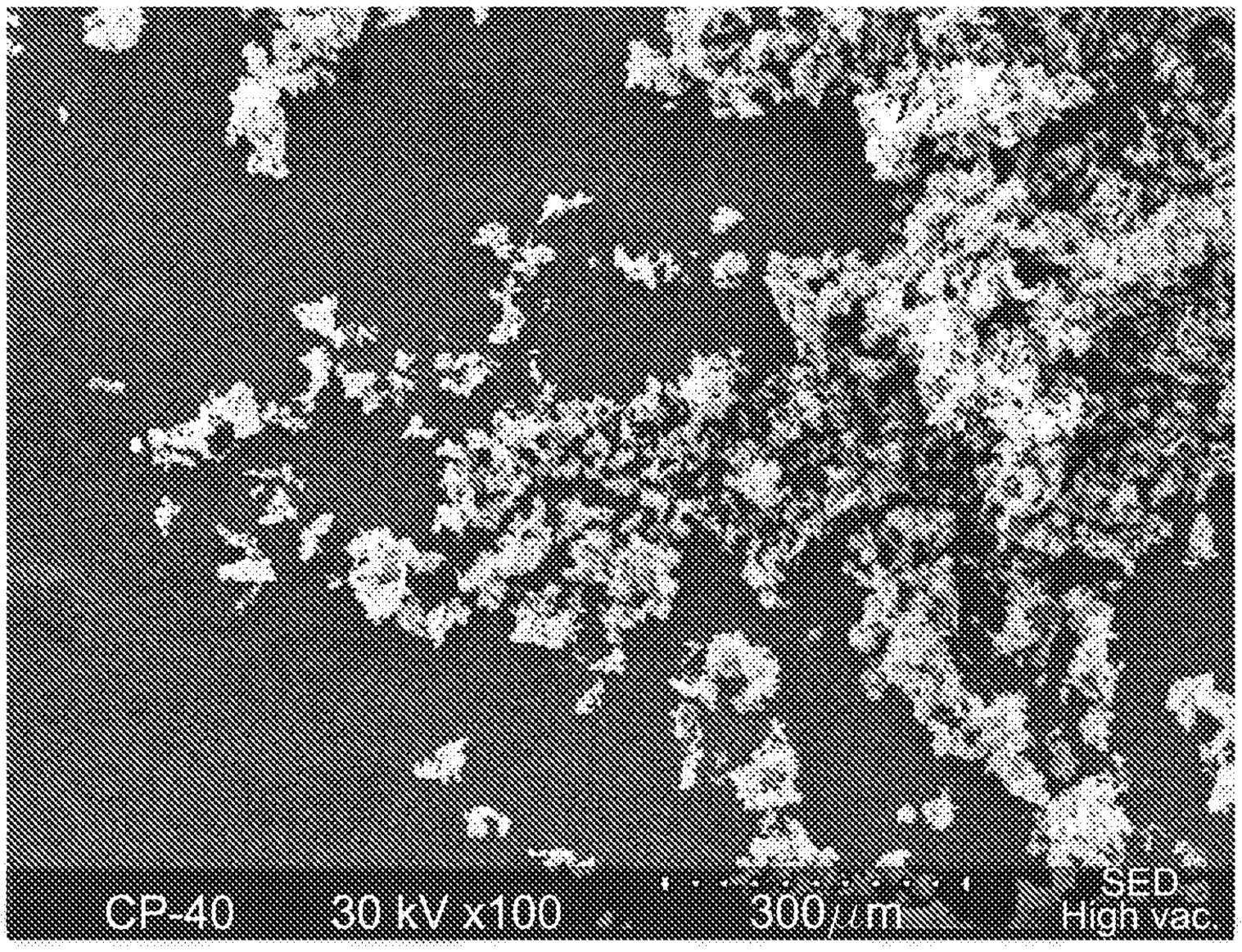


FIG. 17A

Compound 1 Crystal Coated with 2% Aerosil R-972

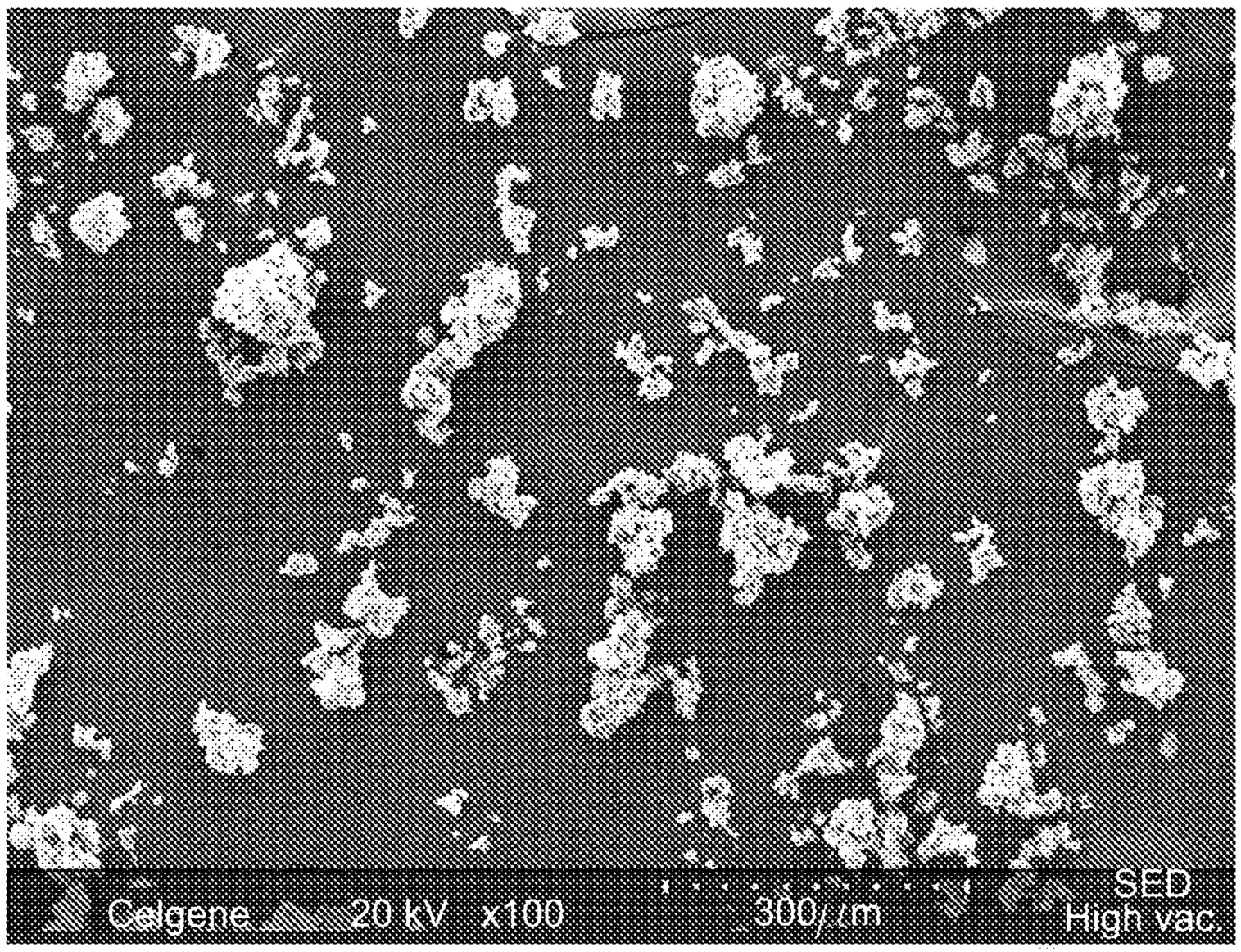


FIG. 17B

Compound 1 Crystal Coated with 5% Aerosil R-972

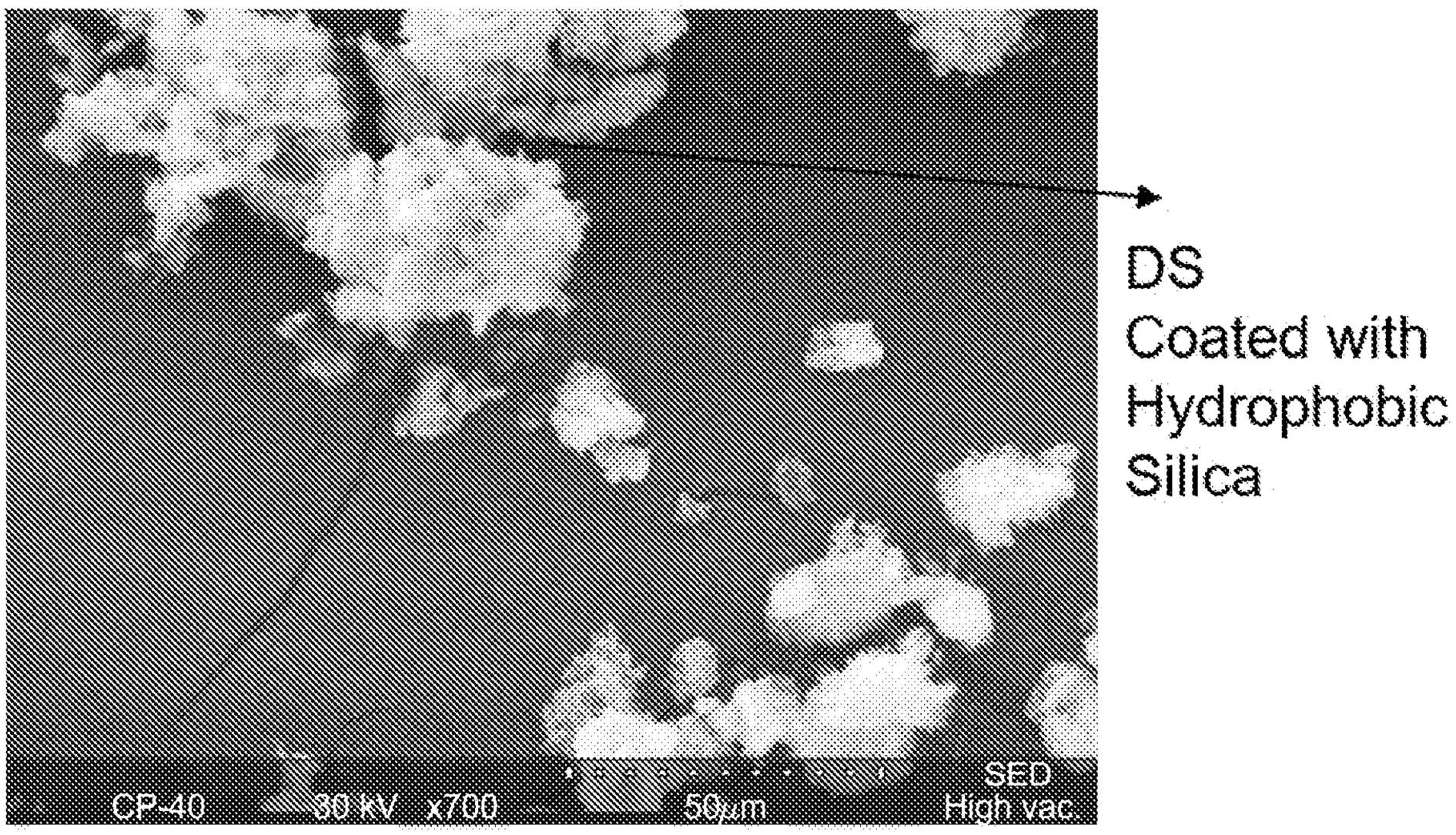


FIG. 18A

Compound 1 Crystal Coated with 5% Aerosil 300

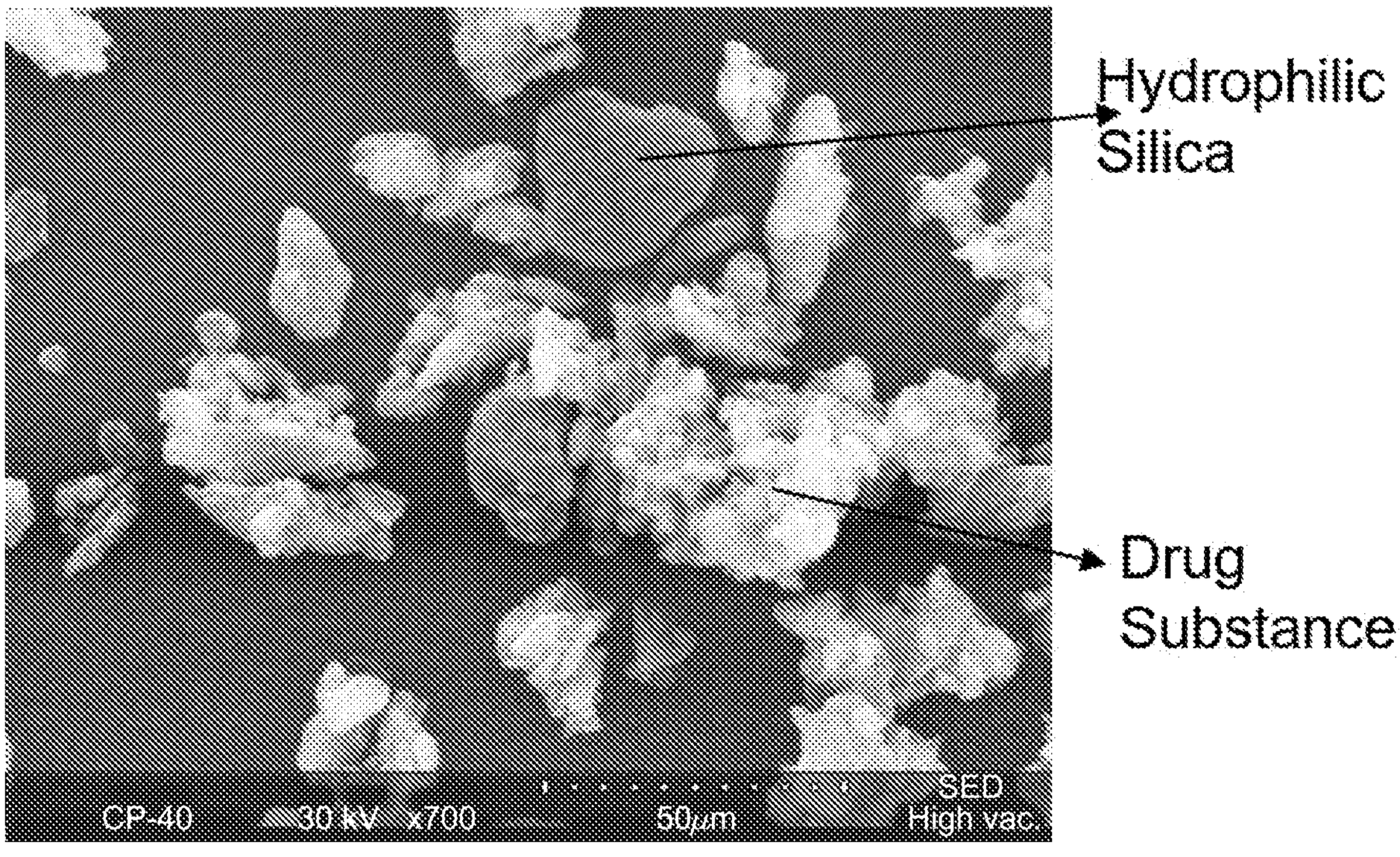


FIG. 18B

Compound 1 Crystal Coated with 5% Aerosil 200

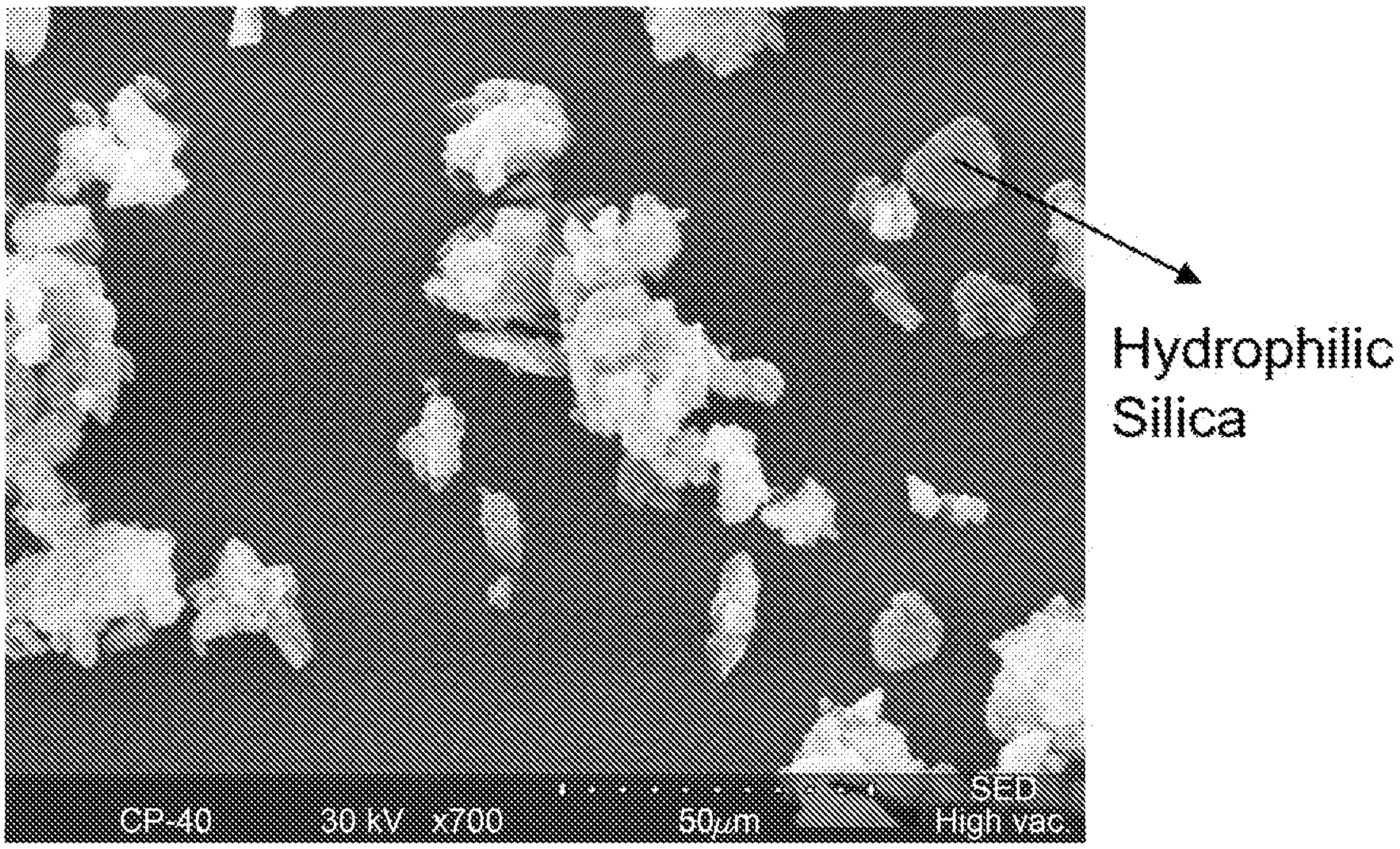


FIG. 18C

Control Without Aerosil

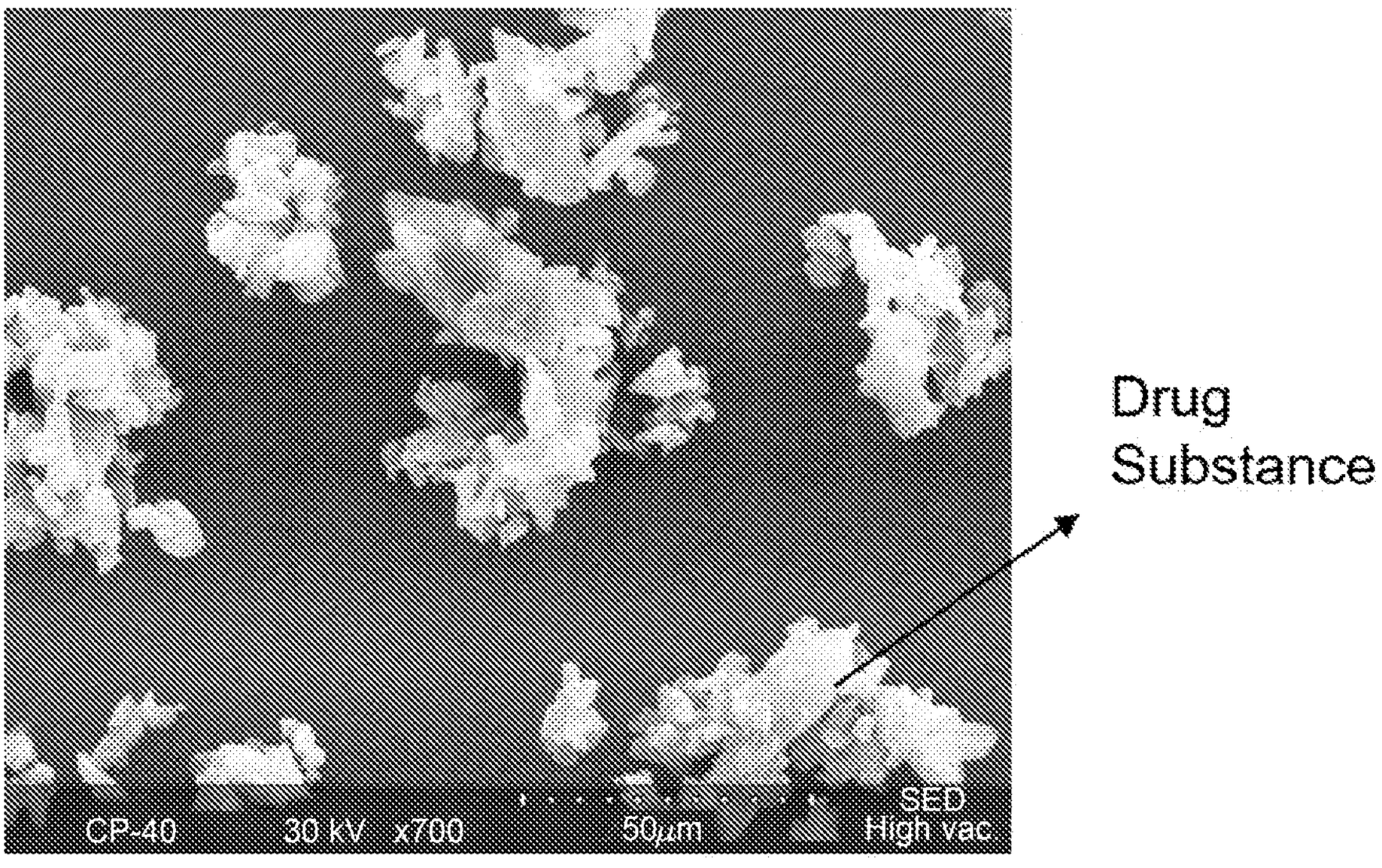


FIG. 18D

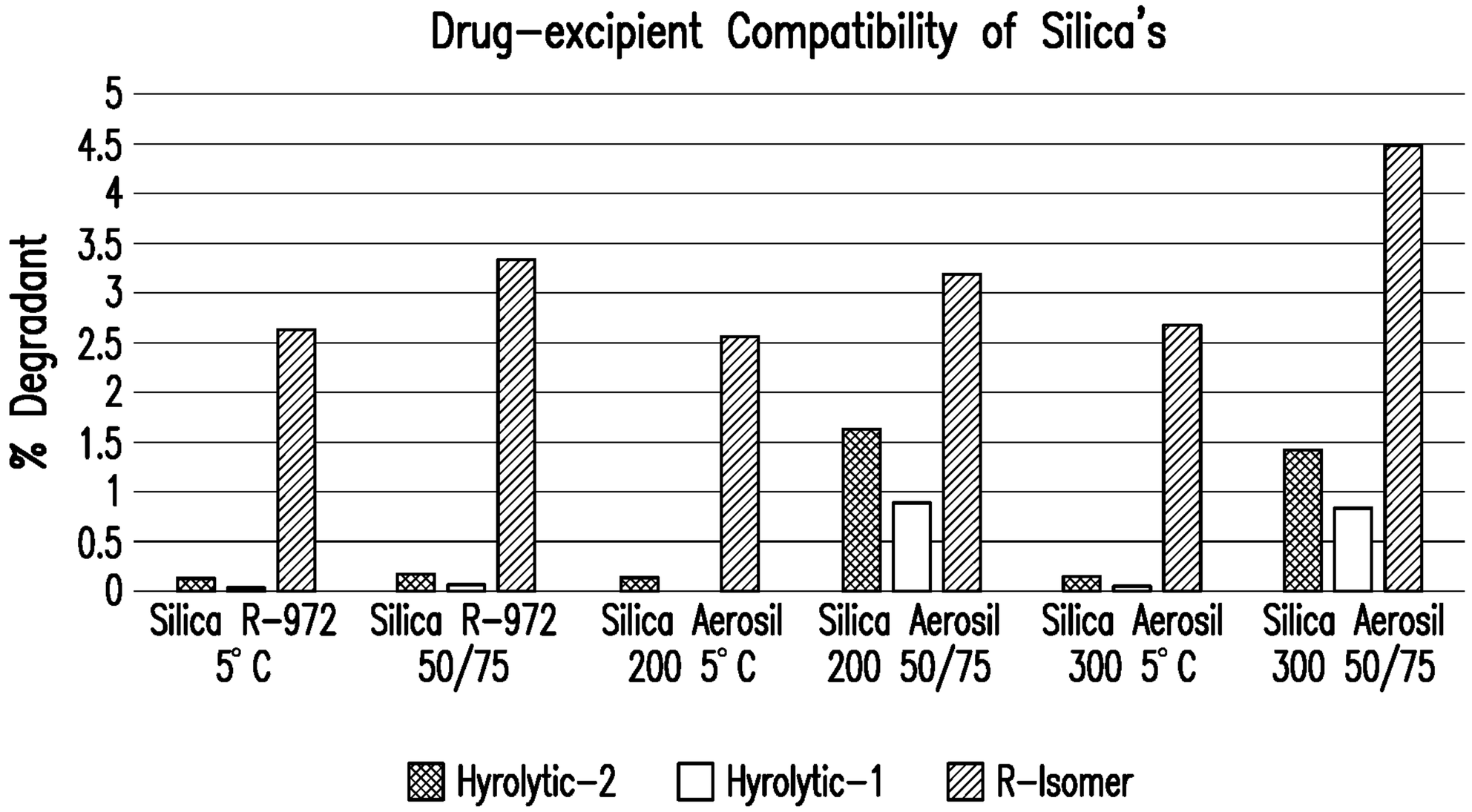

Drug–excipient Compatibility of Silica's
% Degradant
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Silica R–972 5° C
Silica R–972 50/75
Silica Aerosil 200 5° C
Silica Aerosil 200 50/75
Silica Aerosil 300 5° C
Silica Aerosil 300 50/75
Hyrolytic–2
Hyrolytic–1
R–Isomer

FIG. 19

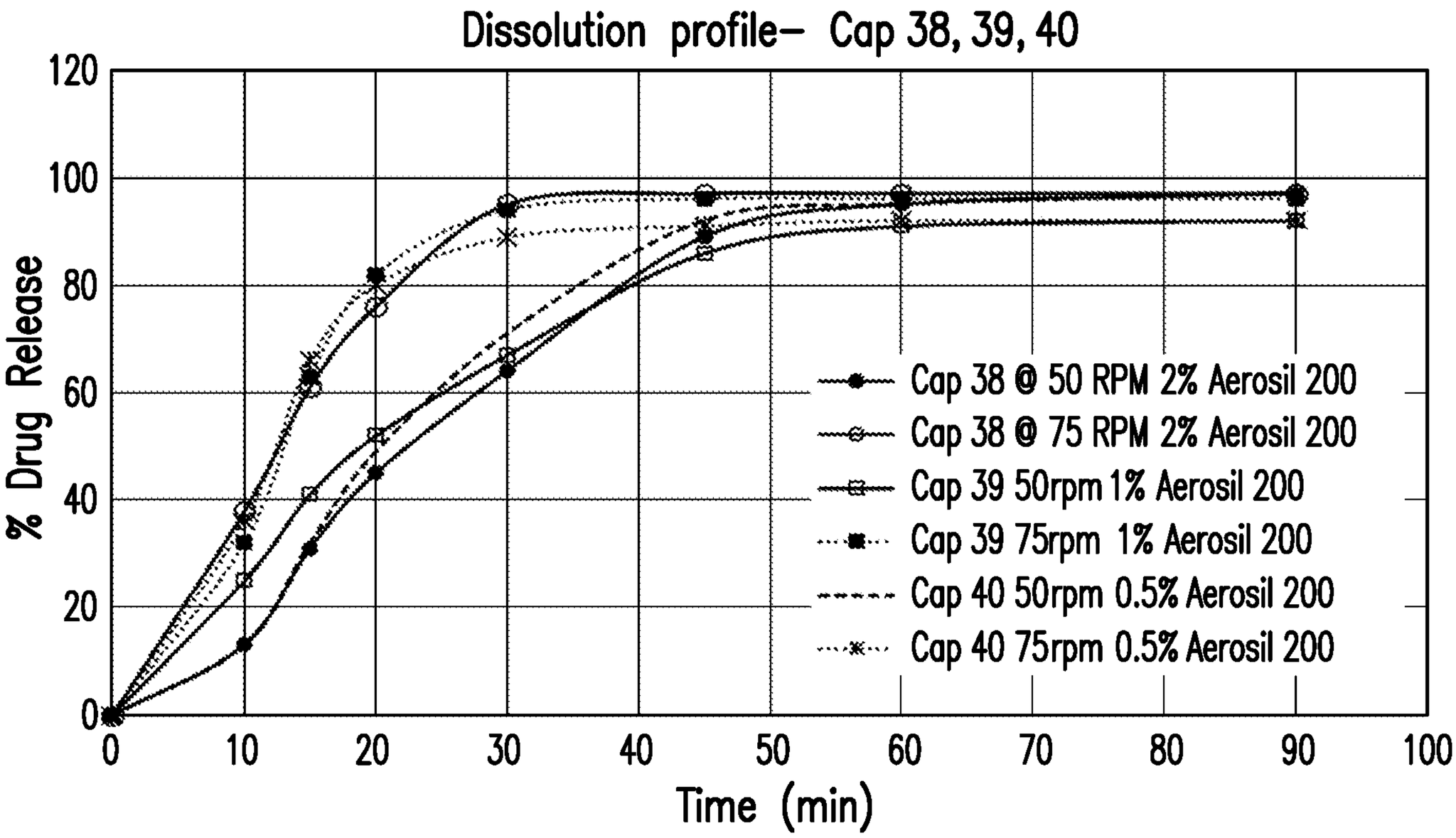

Dissolution profile– Cap 38, 39, 40
% Drug Release
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
Time (min)
Cap 38 @ 50 RPM 2% Aerosil 200
Cap 38 @ 75 RPM 2% Aerosil 200
Cap 39 50rpm 1% Aerosil 200
Cap 39 75rpm 1% Aerosil 200
Cap 40 50rpm 0.5% Aerosil 200
Cap 40 75rpm 0.5% Aerosil 200

FIG. 20

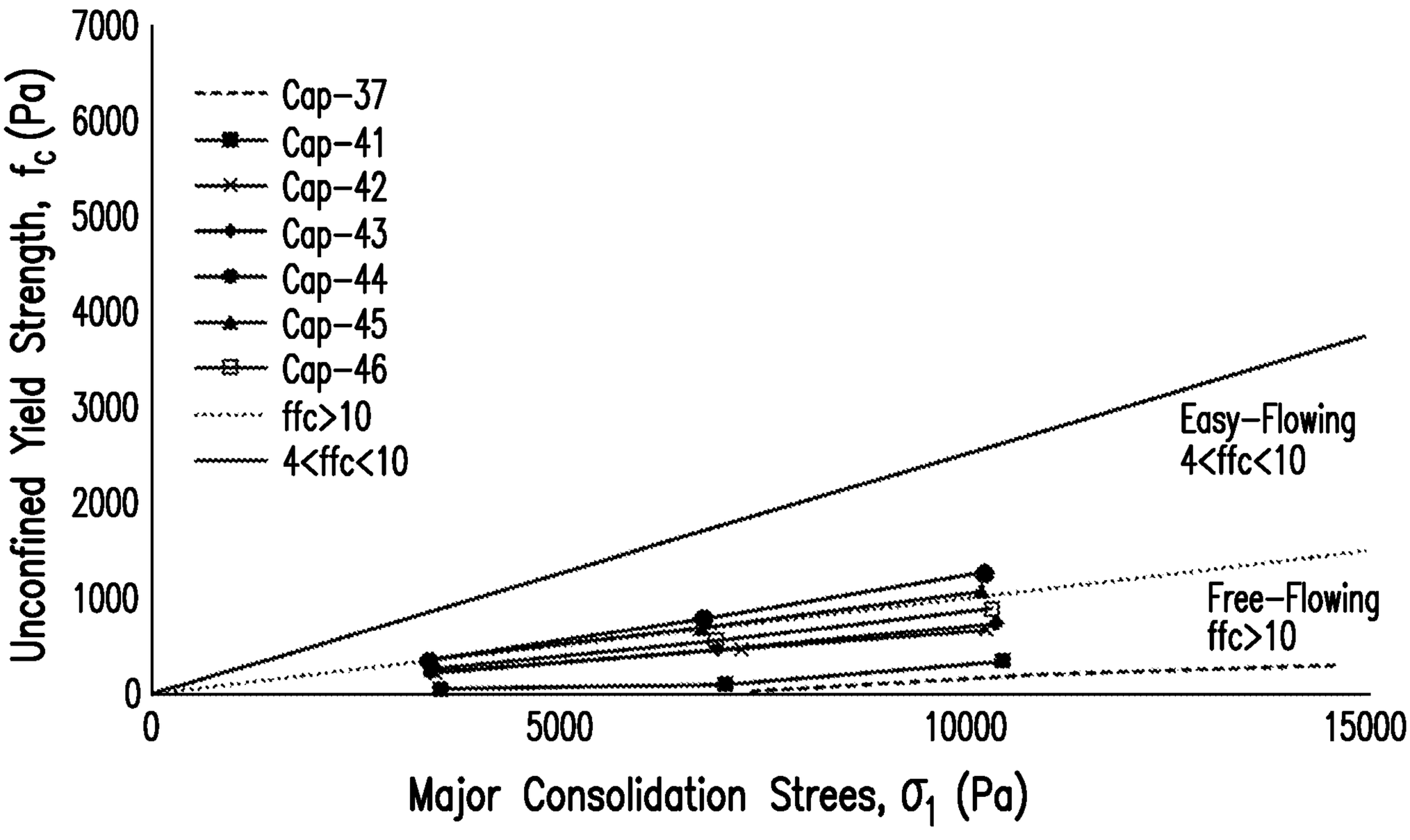

Powder Flow Behavior
Unconfined Yield Strength, f_c (Pa)
7000
6000
5000
4000
3000
2000
1000
0
Cap-37
Cap-41
Cap-42
Cap-43
Cap-44
Cap-45
Cap-46
ffc>10
4<ffc<10
Easy-Flowing
4<ffc<10
Free-Flowing
ffc>10
0
5000
10000
15000
Major Consolidation Strees, σ_1 (Pa)

FIG. 21

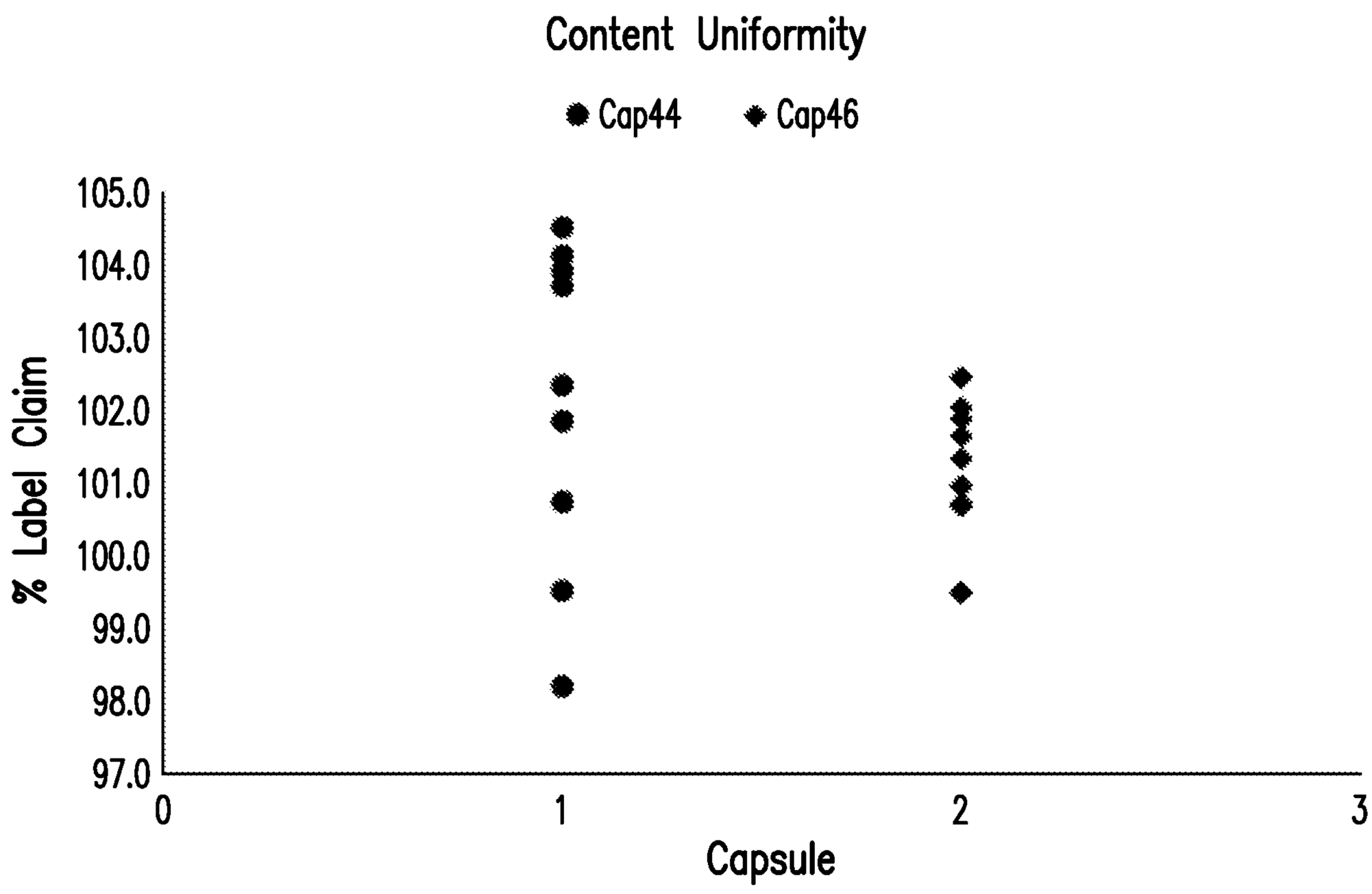

Content Uniformity
Cap44
Cap46
% Label Claim
105.0
104.0
103.0
102.0
101.0
100.0
99.0
98.0
97.0
0
1
2
3
Capsule

FIG. 22

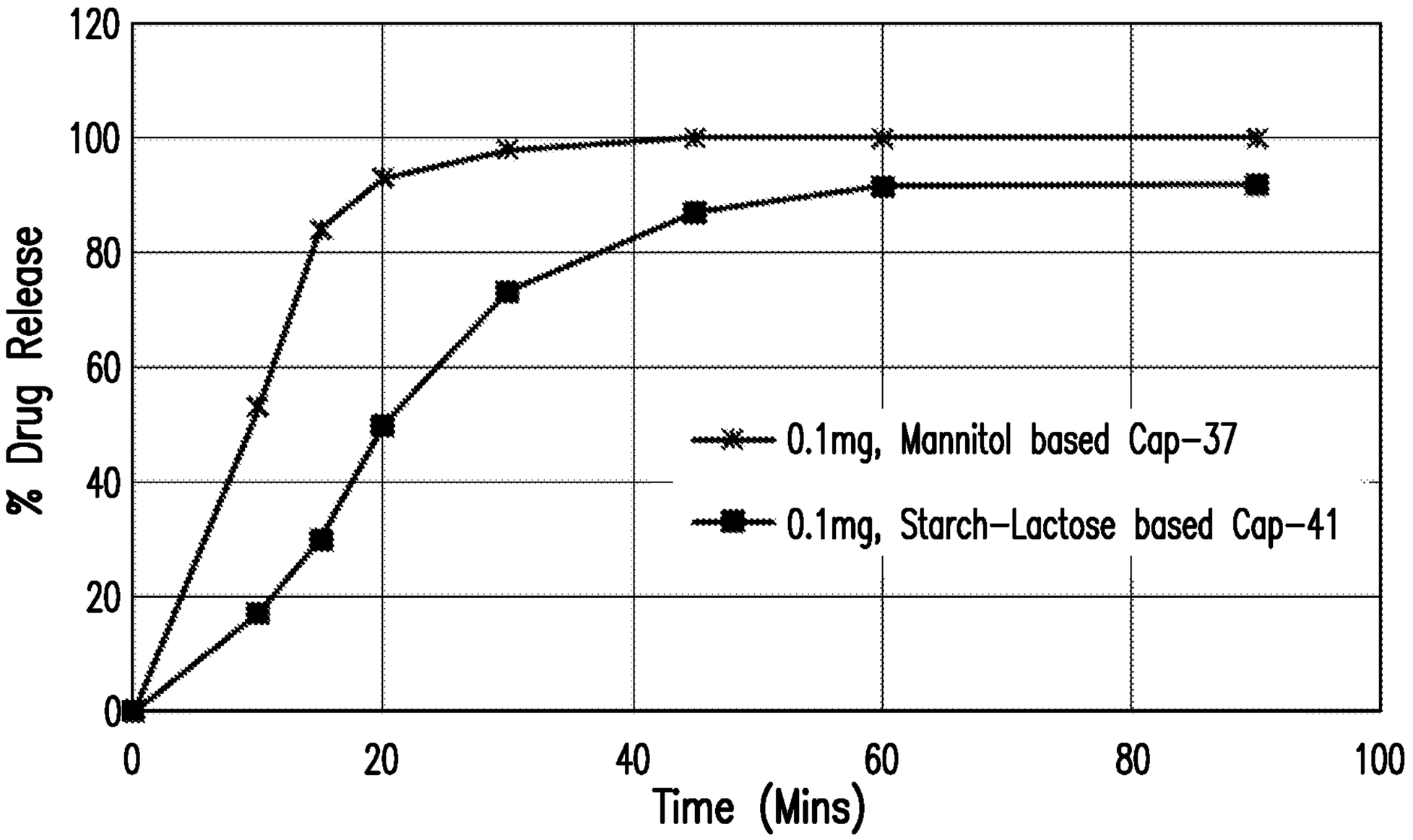

Comparative Dissolution Profiles of 0.1mg Mannitol BIC and Starch-Lactose BIC at T=0
% Drug Release
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (Mins)
0.1mg, Mannitol based Cap-37
0.1mg, Starch-Lactose based Cap-41

FIG. 23

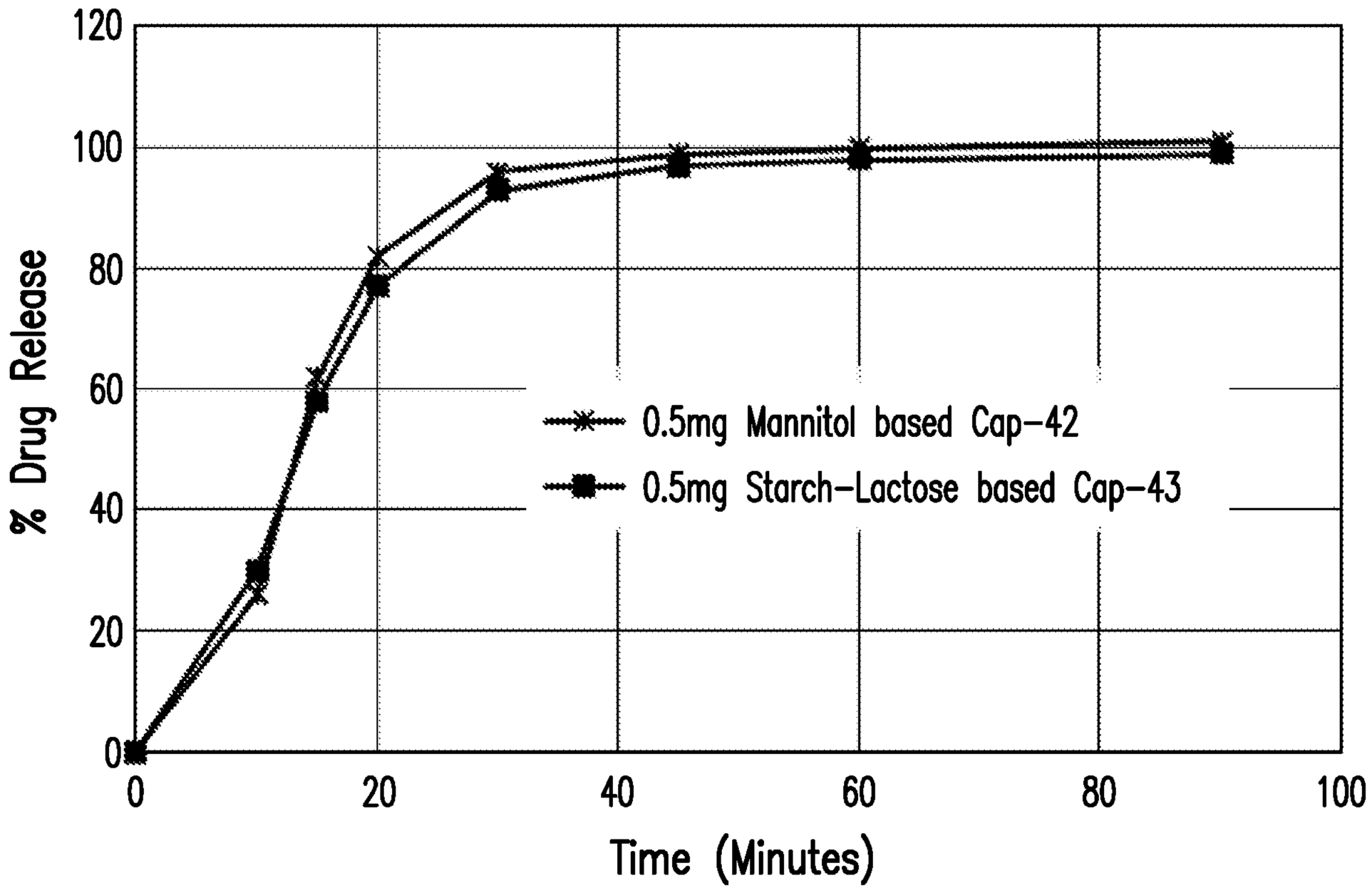

Comparative Dissolution Profiles of 0.5mg Mannitol BIC and Starch-Lactose BIC at T=0
% Drug Release
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (Minutes)
0.5mg Mannitol based Cap-42
0.5mg Starch-Lactose based Cap-43

FIG. 24

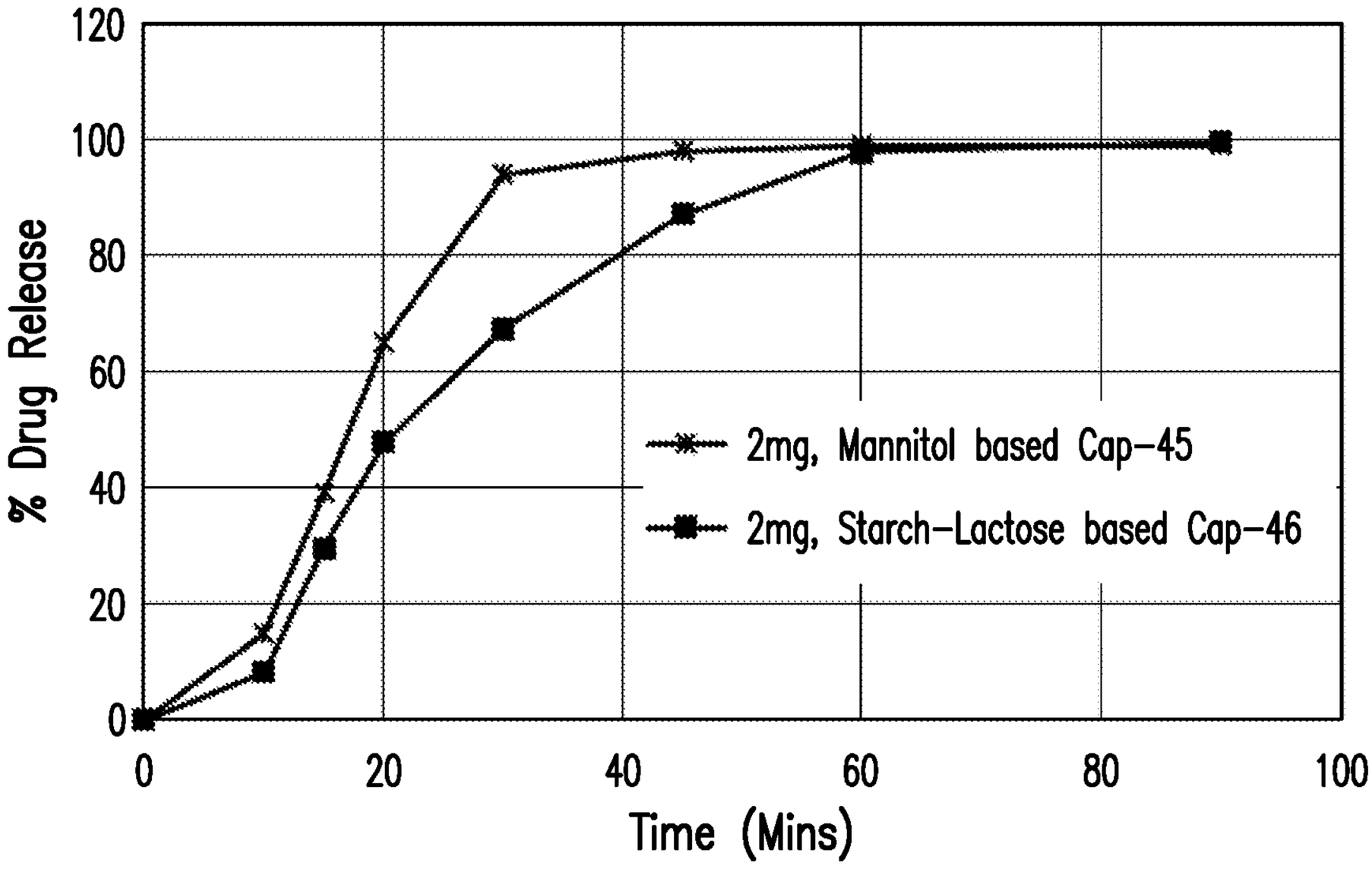

Comparative Dissolution Profiles of 2mg Mannitol BIC and Starch-Lactose BIC at T=0
% Drug Release
Time (Mins)
0
20
40
60
80
100
120
2mg, Mannitol based Cap-45
2mg, Starch-Lactose based Cap-46

FIG. 25

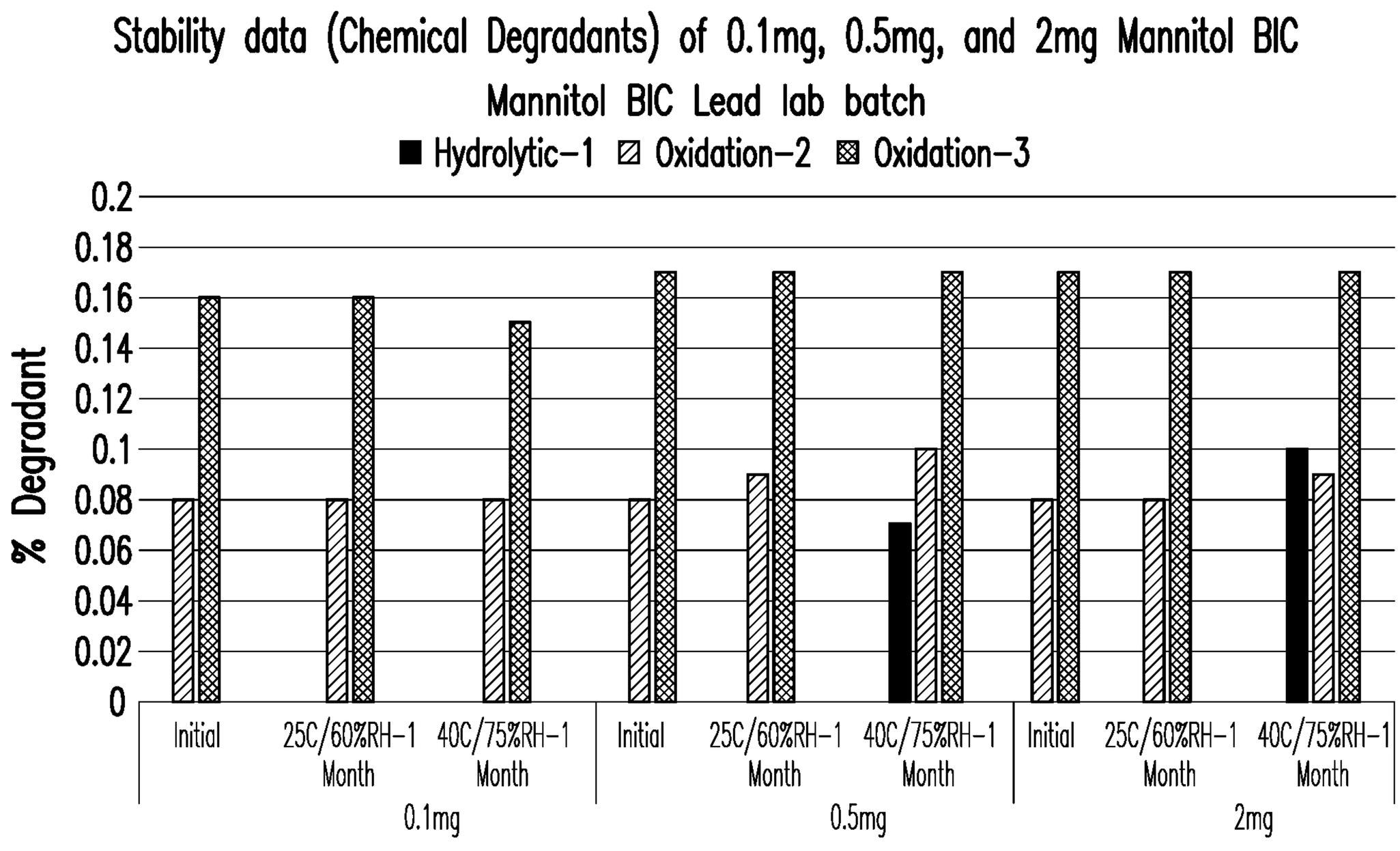

Stability data (Chemical Degradants) of 0.1mg, 0.5mg, and 2mg Mannitol BIC
Mannitol BIC Lead lab batch
Hydrolytic-1
Oxidation-2
Oxidation-3
% Degradant
0.2
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
Initial
25C/60%RH-1 Month
40C/75%RH-1 Month
0.1mg
0.5mg
2mg

FIG. 26

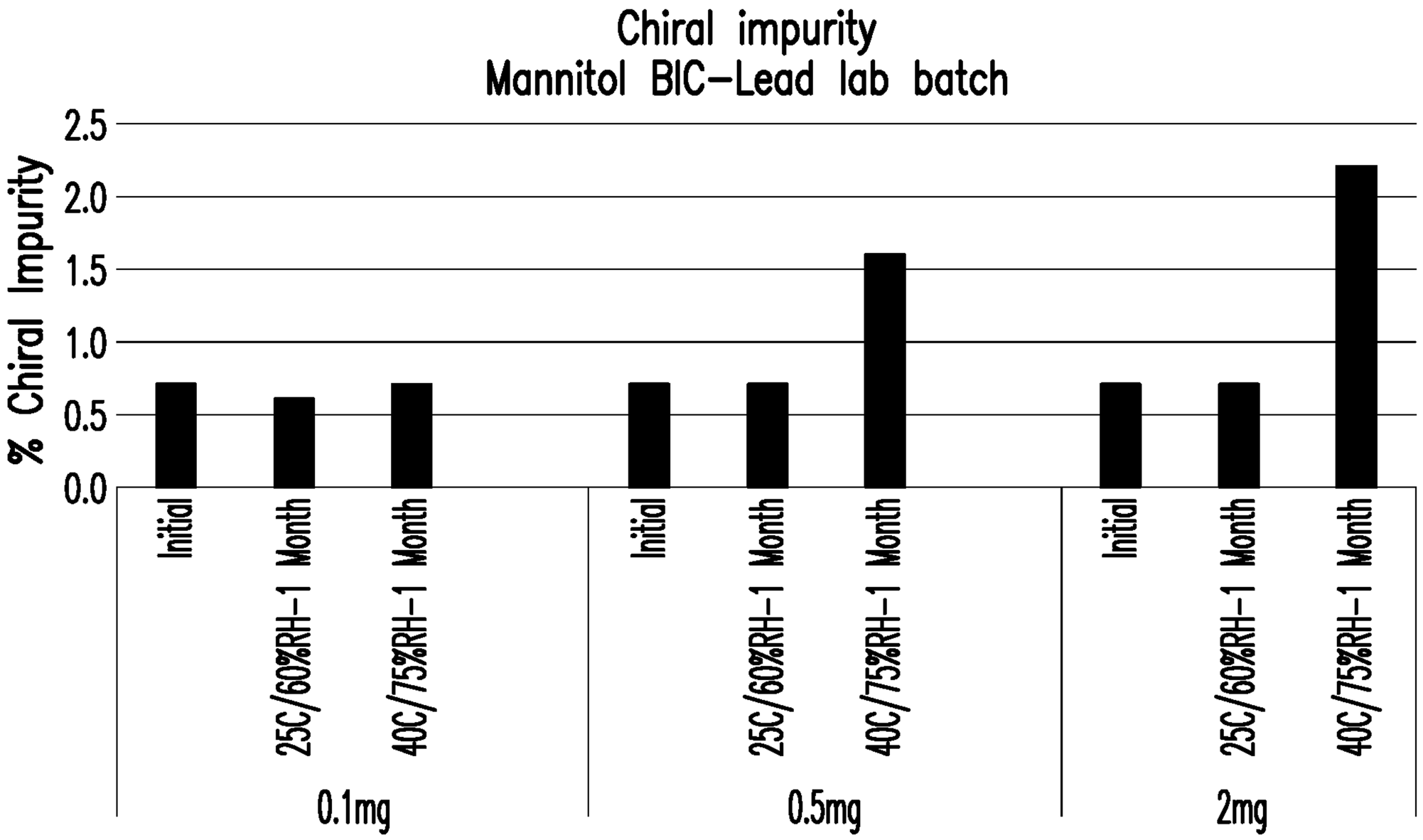

Chiral impurity
Mannitol BIC–Lead lab batch
% Chiral Impurity
2.5
2.0
1.5
1.0
0.5
0.0
Initial
25C/60%RH–1 Month
40C/75%RH–1 Month
0.1mg
0.5mg
2mg

FIG. 27

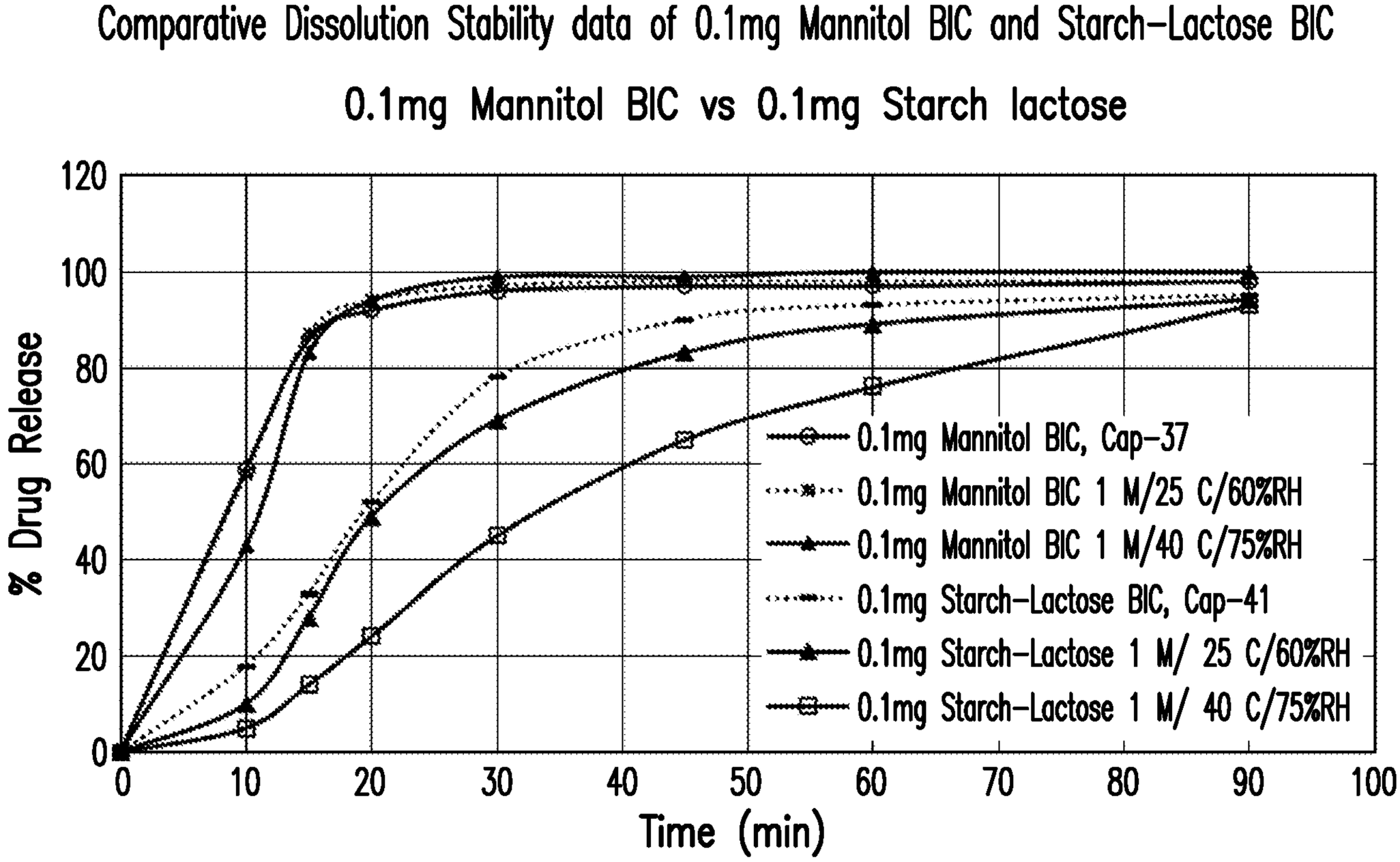

Comparative Dissolution Stability data of 0.1mg Mannitol BIC and Starch–Lactose BIC
0.1mg Mannitol BIC vs 0.1mg Starch lactose
% Drug Release
120
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
Time (min)
0.1mg Mannitol BIC, Cap–37
0.1mg Mannitol BIC 1 M/25 C/60%RH
0.1mg Mannitol BIC 1 M/40 C/75%RH
0.1mg Starch–Lactose BIC, Cap–41
0.1mg Starch–Lactose 1 M/ 25 C/60%RH
0.1mg Starch–Lactose 1 M/ 40 C/75%RH

FIG. 28

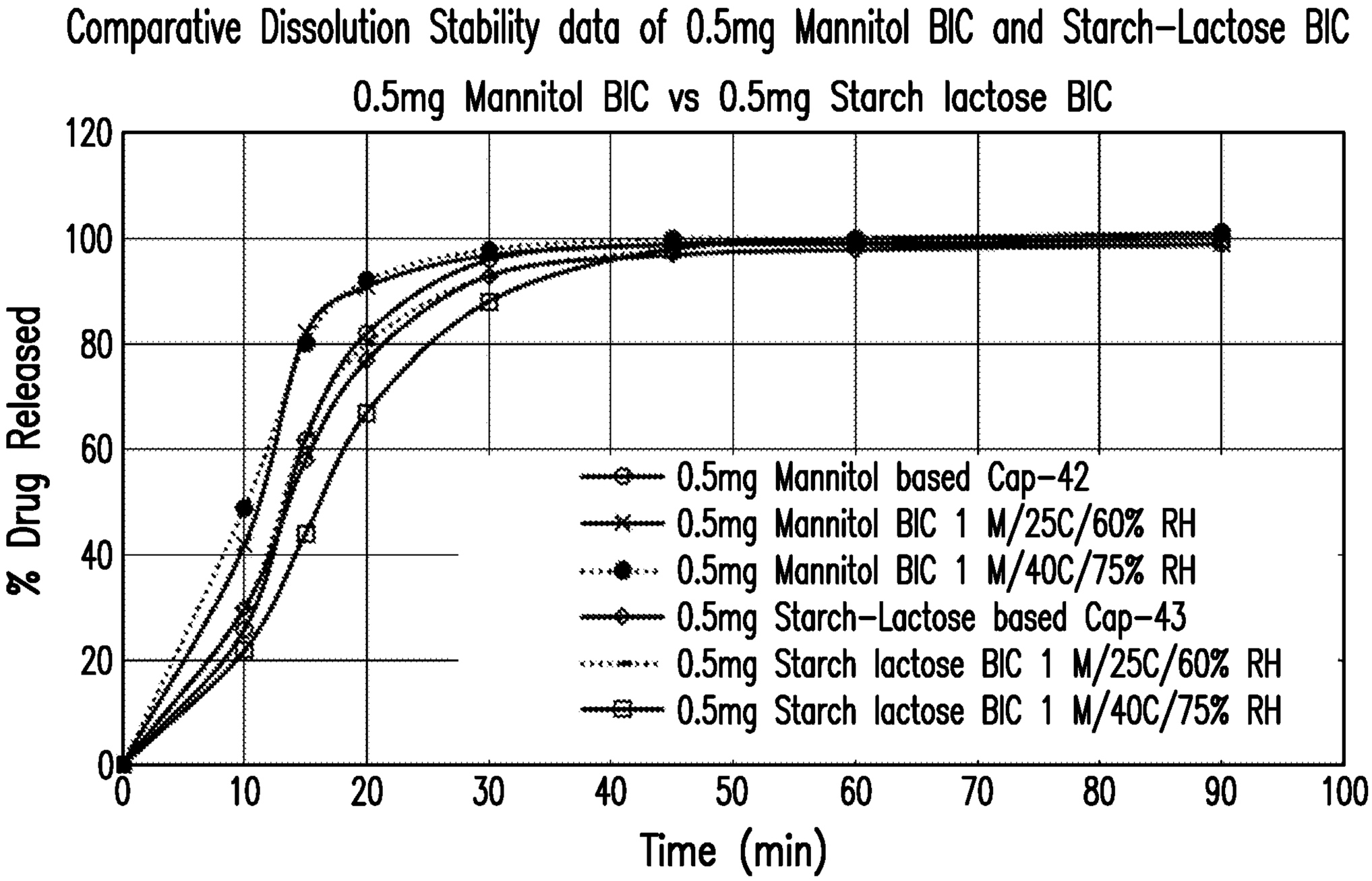

Comparative Dissolution Stability data of 0.5mg Mannitol BIC and Starch-Lactose BIC
0.5mg Mannitol BIC vs 0.5mg Starch lactose BIC
% Drug Released
Time (min)
0.5mg Mannitol based Cap-42
0.5mg Mannitol BIC 1 M/25C/60% RH
0.5mg Mannitol BIC 1 M/40C/75% RH
0.5mg Starch-Lactose based Cap-43
0.5mg Starch lactose BIC 1 M/25C/60% RH
0.5mg Starch lactose BIC 1 M/40C/75% RH

FIG. 29

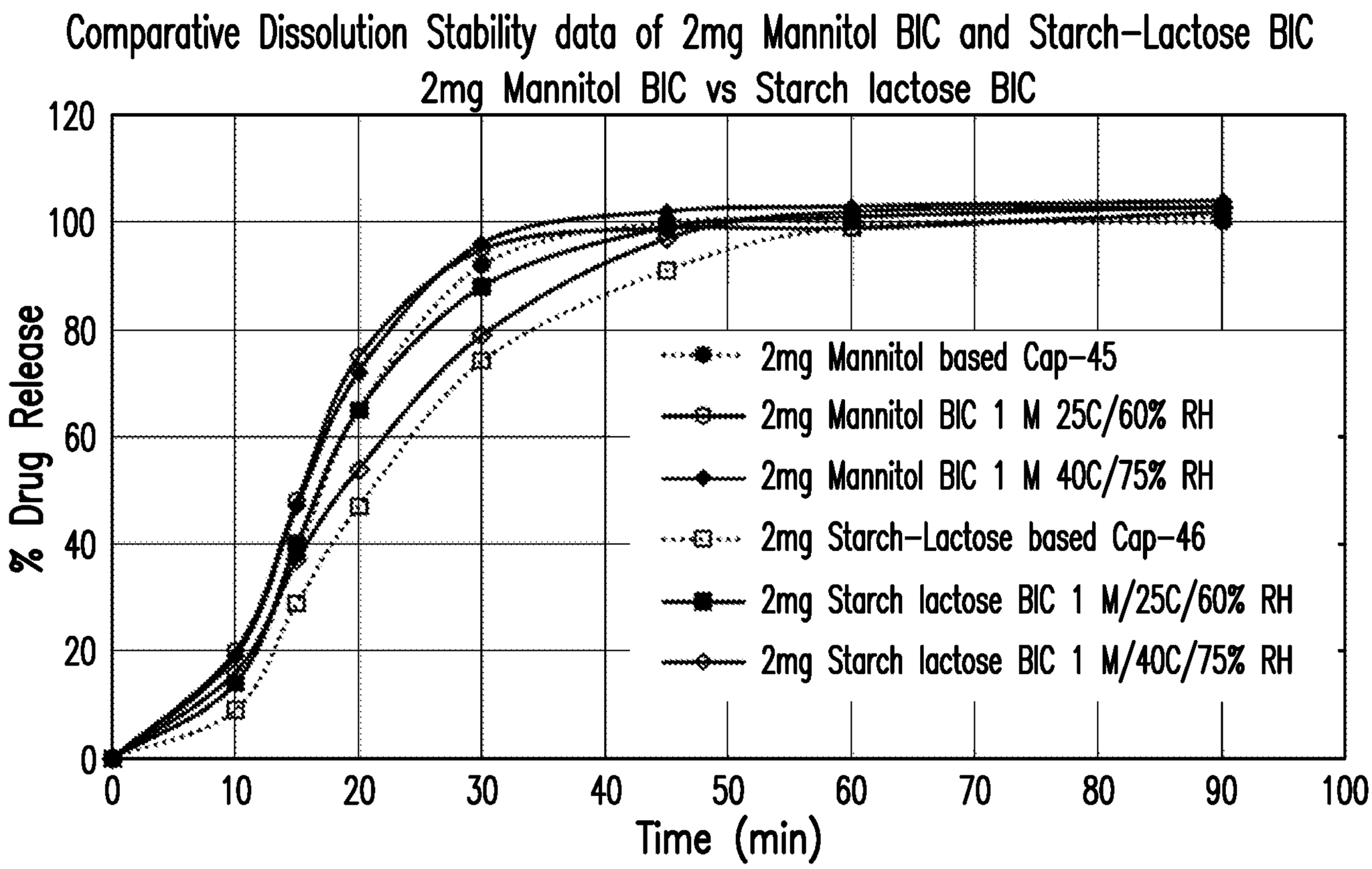

Comparative Dissolution Stability data of 2mg Mannitol BIC and Starch-Lactose BIC
2mg Mannitol BIC vs Starch lactose BIC
% Drug Release
Time (min)
2mg Mannitol based Cap-45
2mg Mannitol BIC 1 M 25C/60% RH
2mg Mannitol BIC 1 M 40C/75% RH
2mg Starch-Lactose based Cap-46
2mg Starch lactose BIC 1 M/25C/60% RH
2mg Starch lactose BIC 1 M/40C/75% RH

FIG. 30