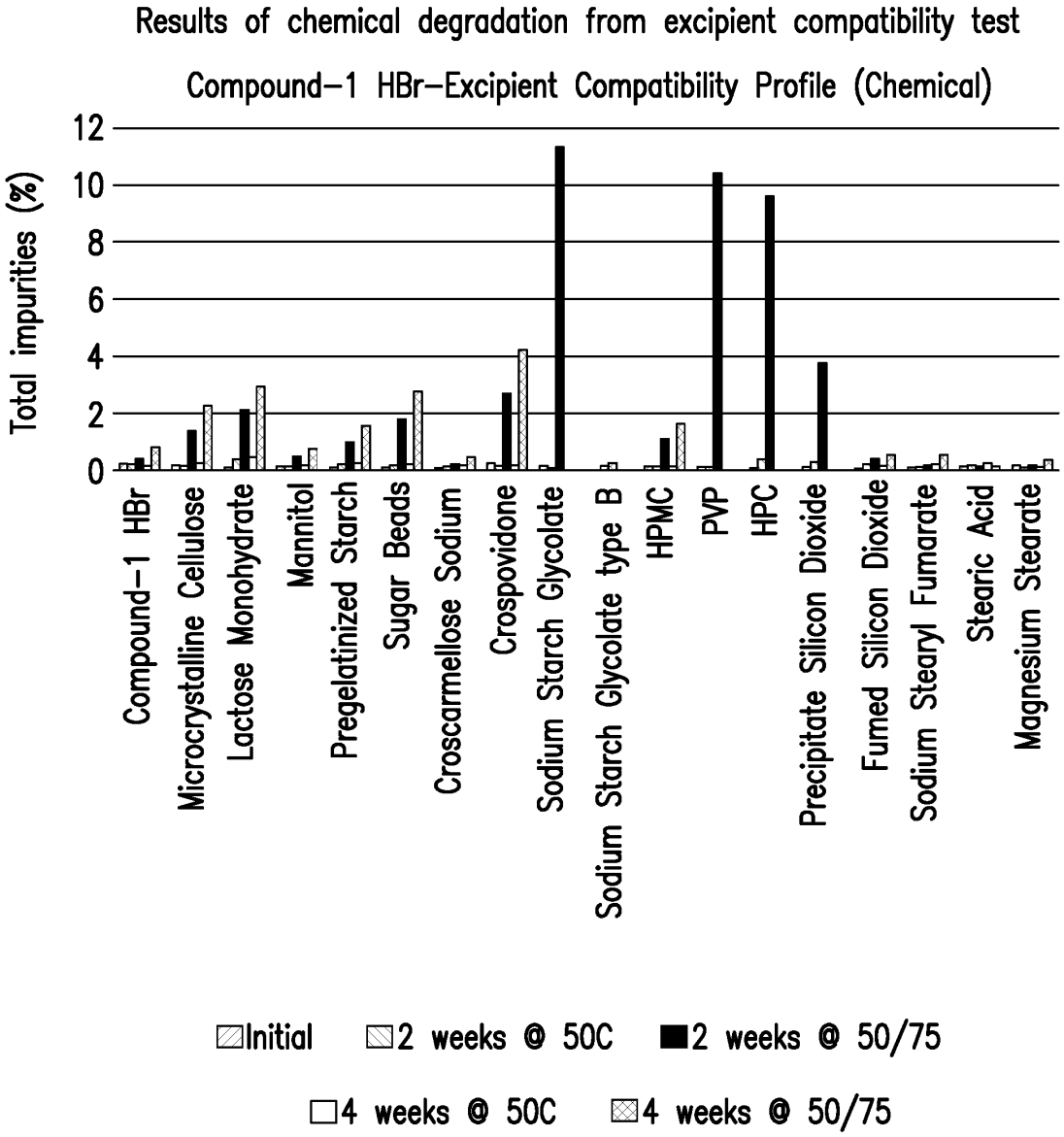

Results of chemical degradation from excipient compatibility test
Compound–1 HBr–Excipient Compatibility Profile (Chemical)
Total impurities (%)
12
10
8
6
4
2
0
Compound–1 HBr
Microcrystalline Cellulose
Lactose Monohydrate
Mannitol
Pregelatinized Starch
Sugar Beads
Croscarmellose Sodium
Crospovidone
Sodium Starch Glycolate
Sodium Starch Glycolate type B
HPMC
PVP
HPC
Precipitate Silicon Dioxide
Fumed Silicon Dioxide
Sodium Stearyl Fumarate
Stearic Acid
Magnesium Stearate
Initial
2 weeks @ 50C
2 weeks @ 50/75
4 weeks @ 50C
4 weeks @ 50/75

FIG. 1A

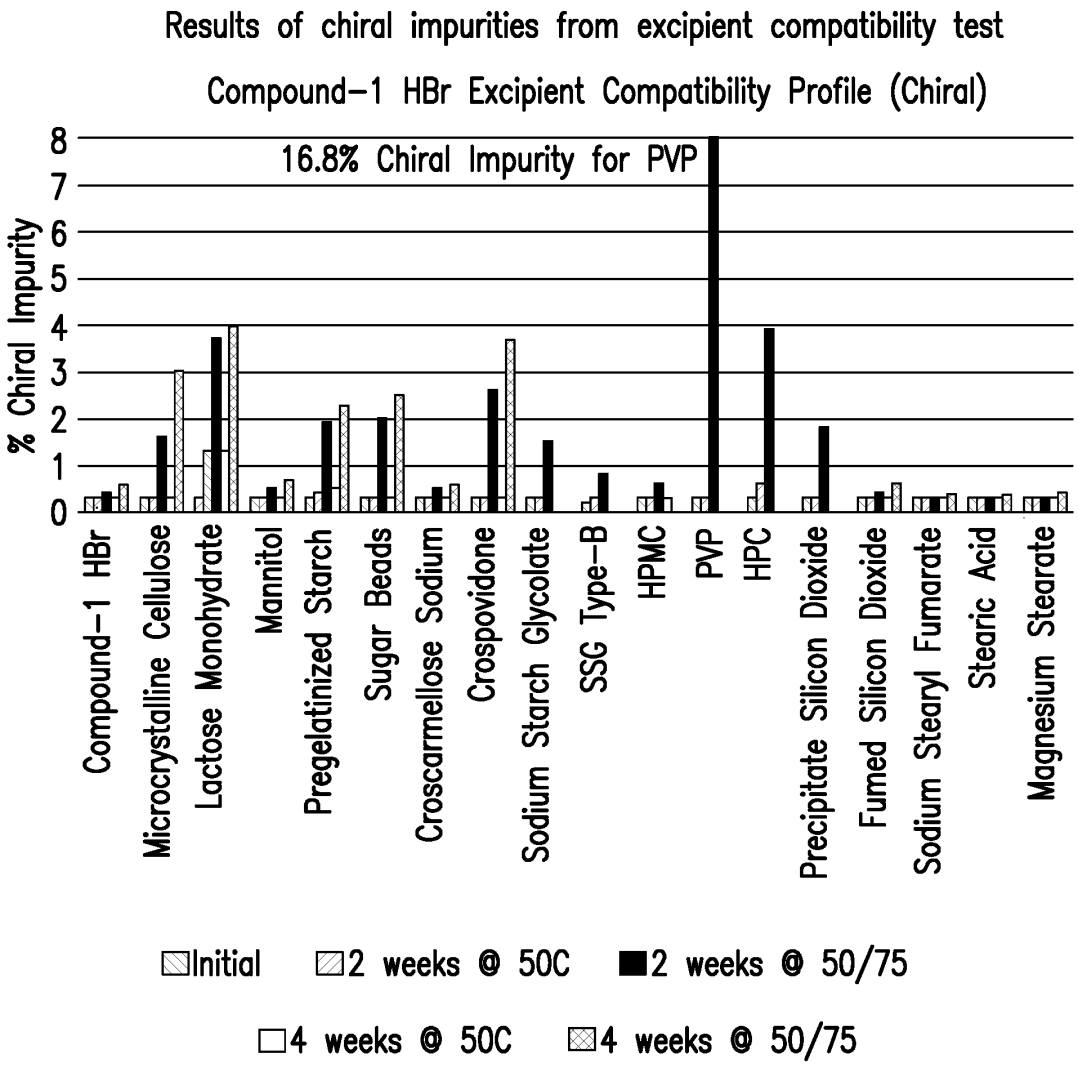

Results of chiral impurities from excipient compatibility test
Compound-1 HBr Excipient Compatibility Profile (Chiral)
16.8% Chiral Impurity for PVP
% Chiral Impurity
0
1
2
3
4
5
6
7
8
Compound-1 HBr
Microcrystalline Cellulose
Lactose Monohydrate
Mannitol
Pregelatinized Starch
Sugar Beads
Croscarmellose Sodium
Crospovidone
Sodium Starch Glycolate
SSG Type-B
HPMC
PVP
HPC
Precipitate Silicon Dioxide
Fumed Silicon Dioxide
Sodium Stearyl Fumarate
Stearic Acid
Magnesium Stearate
Initial
2 weeks @ 50C
2 weeks @ 50/75
4 weeks @ 50C
4 weeks @ 50/75

FIG. 1B

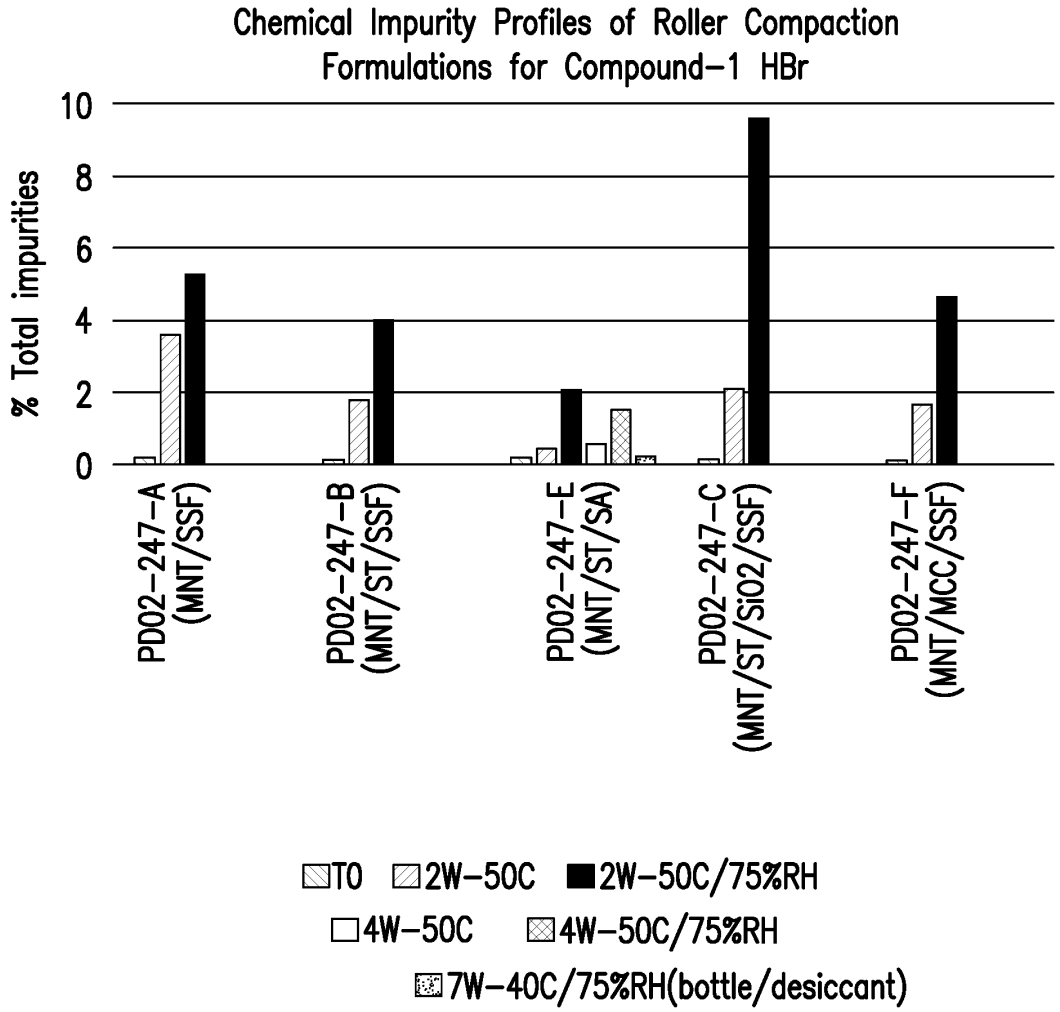

Chemical Impurity Profiles of Roller Compaction Formulations for Compound-1 HBr
% Total impurities
10
8
6
4
2
0
PD02-247-A (MNT/SSF)
PD02-247-B (MNT/ST/SSF)
PD02-247-E (MNT/ST/SA)
PD02-247-C (MNT/ST/SiO2/SSF)
PD02-247-F (MNT/MCC/SSF)
T0
2W-50C
2W-50C/75%RH
4W-50C
4W-50C/75%RH
7W-40C/75%RH(bottle/desiccant)

FIG. 2A

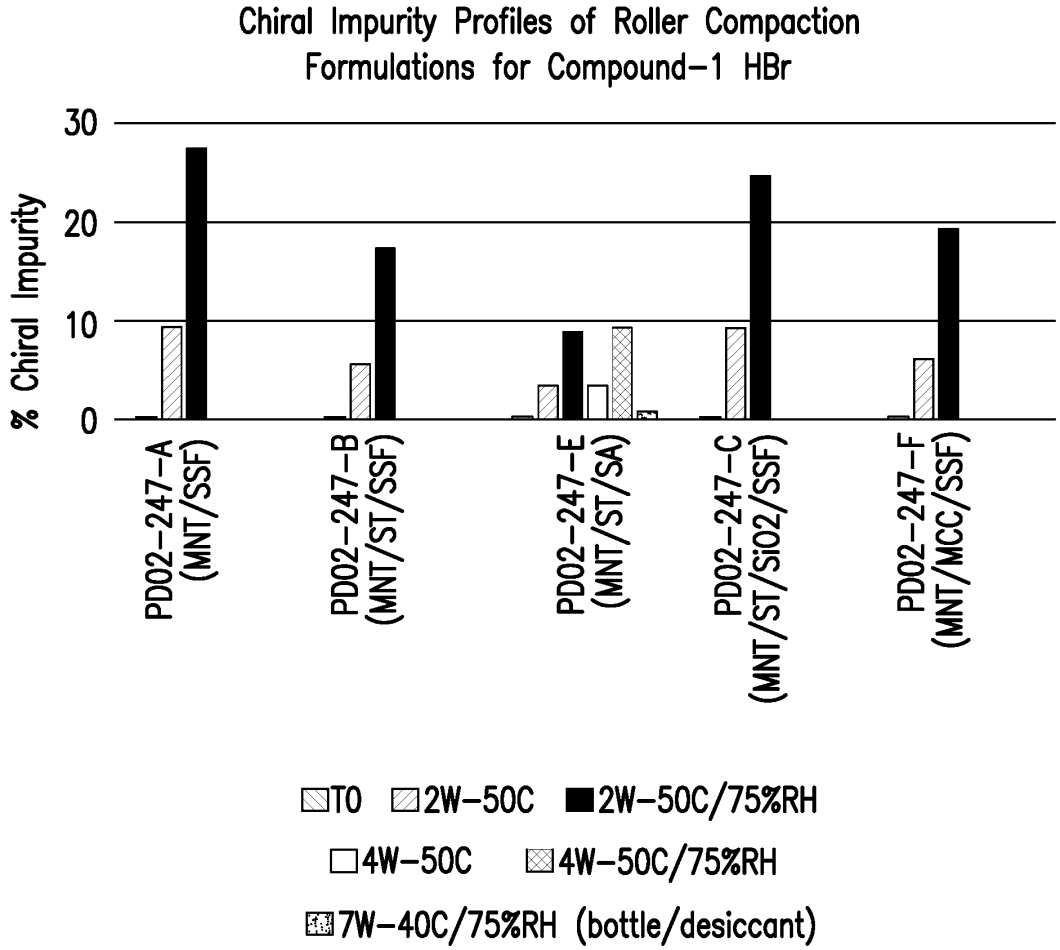

Chiral Impurity Profiles of Roller Compaction Formulations for Compound-1 HBr
% Chiral Impurity
30
20
10
0
PD02-247-A (MNT/SSF)
PD02-247-B (MNT/ST/SSF)
PD02-247-E (MNT/ST/SA)
PD02-247-C (MNT/ST/SiO2/SSF)
PD02-247-F (MNT/MCC/SSF)
T0
2W-50C
2W-50C/75%RH
4W-50C
4W-50C/75%RH
7W-40C/75%RH (bottle/desiccant)

FIG. 2B

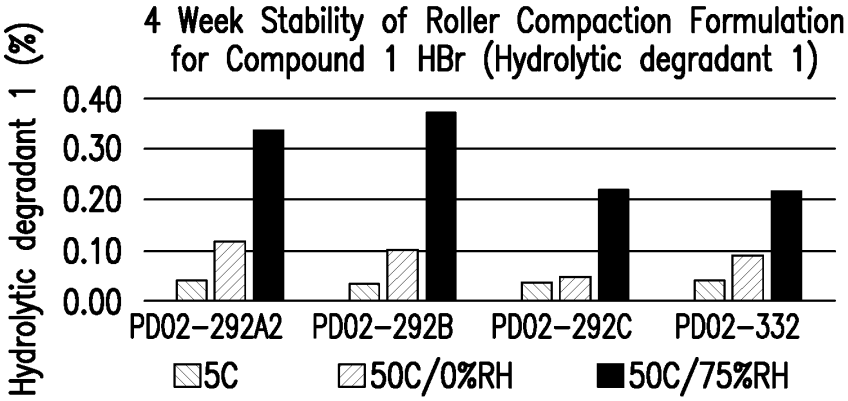


FIG. 3A

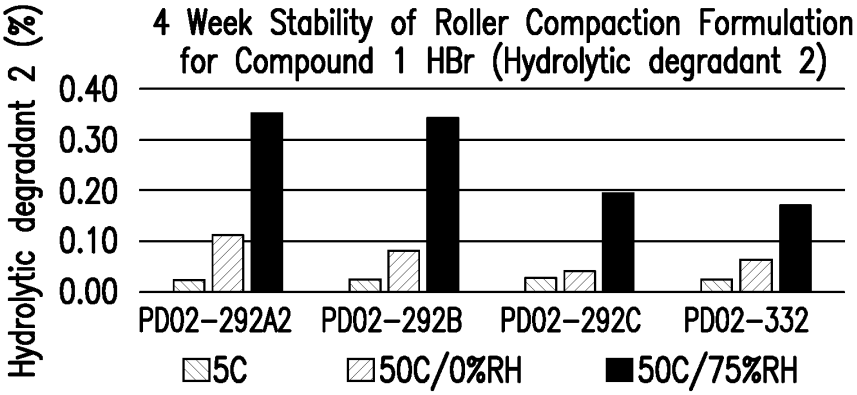


FIG. 3B

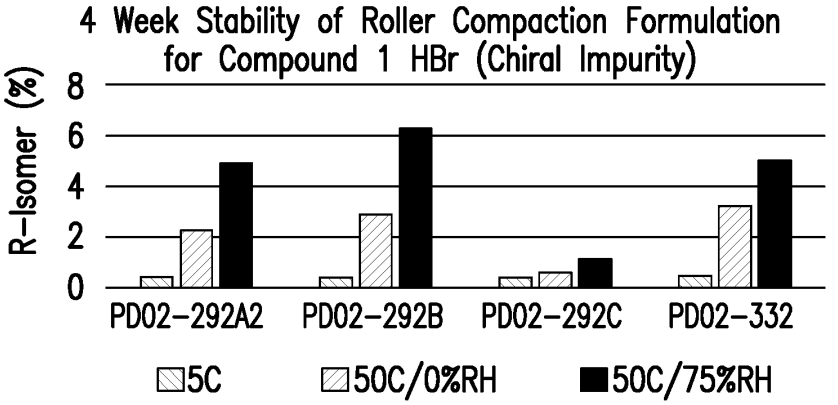


FIG. 3C

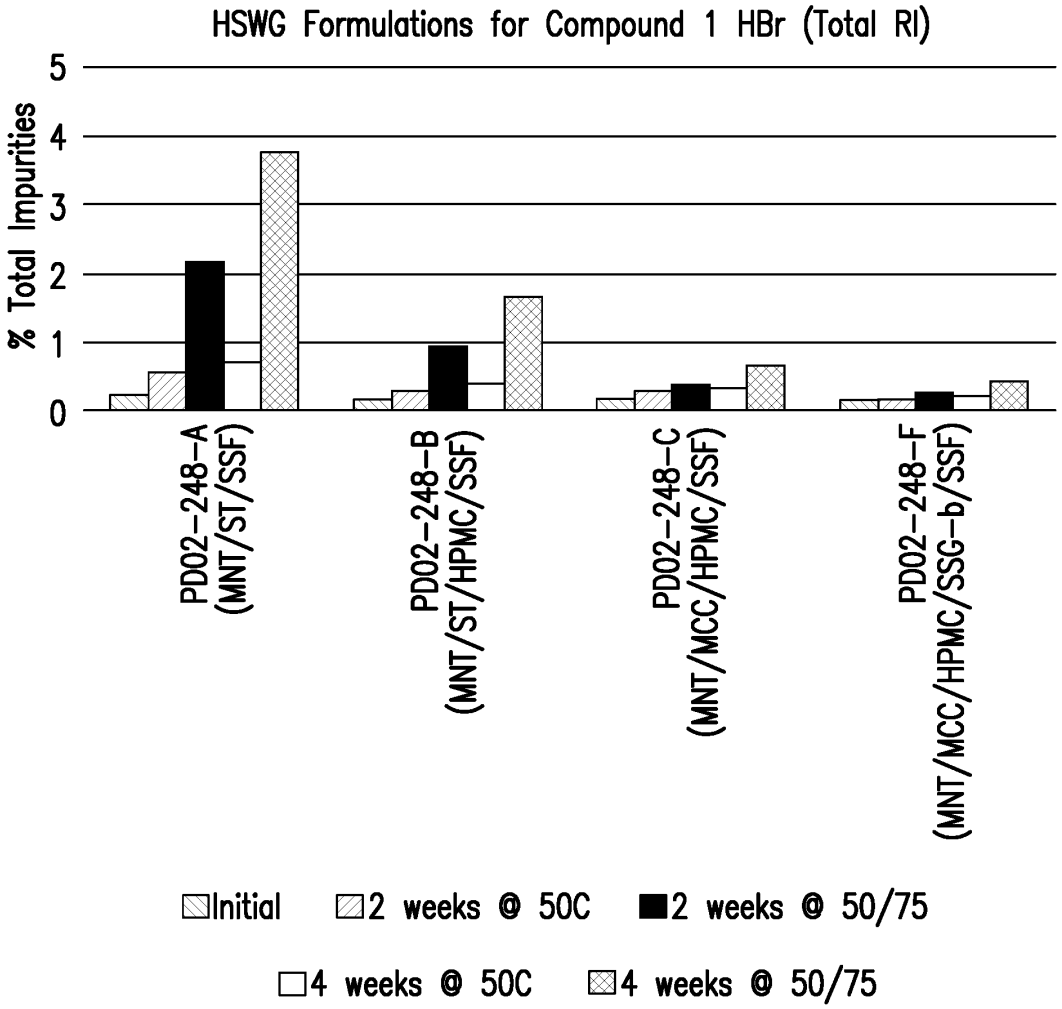

HSWG Formulations for Compound 1 HBr (Total RI)
% Total Impurities
5
4
3
2
1
0
PD02-248-A (MNT/ST/SSF)
PD02-248-B (MNT/ST/HPMC/SSF)
PD02-248-C (MNT/MCC/HPMC/SSF)
PD02-248-F (MNT/MCC/HPMC/SSG-b/SSF)
Initial
2 weeks @ 50C
2 weeks @ 50/75
4 weeks @ 50C
4 weeks @ 50/75

FIG. 4A

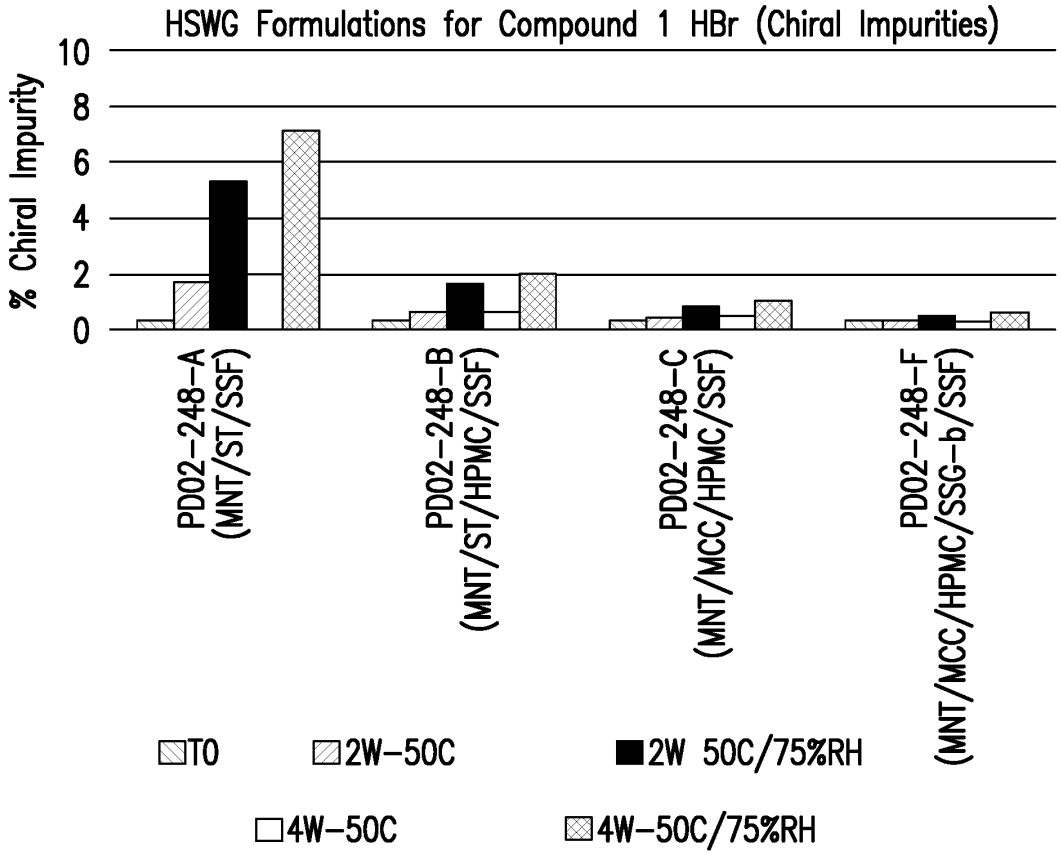

HSWG Formulations for Compound 1 HBr (Chiral Impurities)
% Chiral Impurity
10
8
6
4
2
0
PD02-248-A (MNT/ST/SSF)
PD02-248-B (MNT/ST/HPMC/SSF)
PD02-248-C (MNT/MCC/HPMC/SSF)
PD02-248-F (MNT/MCC/HPMC/SSG-b/SSF)
T0
2W-50C
2W 50C/75%RH
4W-50C
4W-50C/75%RH

FIG. 4B

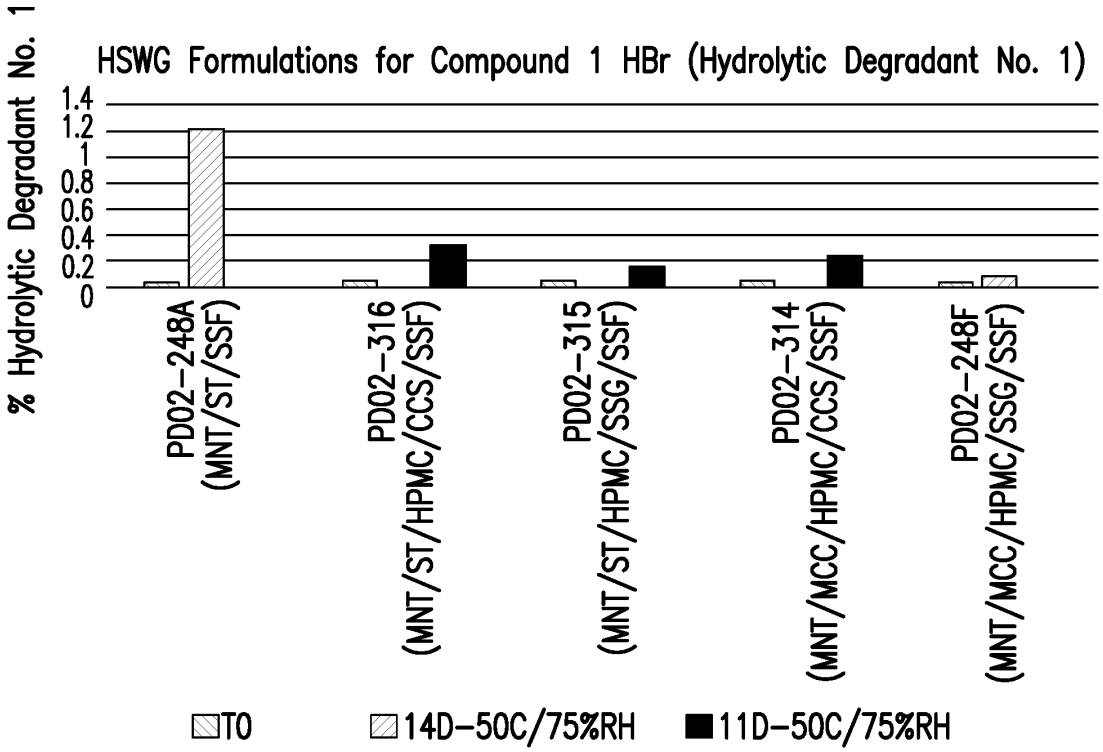

HSWG Formulations for Compound 1 HBr (Hydrolytic Degradant No. 1)
% Hydrolytic Degradant No. 1
1.4
1.2
1
0.8
0.6
0.4
0.2
0
PD02-248A (MNT/ST/SSF)
PD02-316 (MNT/ST/HPMC/CCS/SSF)
PD02-315 (MNT/ST/HPMC/SSG/SSF)
PD02-314 (MNT/MCC/HPMC/CCS/SSF)
PD02-248F (MNT/MCC/HPMC/SSG/SSF)
T0
14D-50C/75%RH
11D-50C/75%RH

FIG. 5A

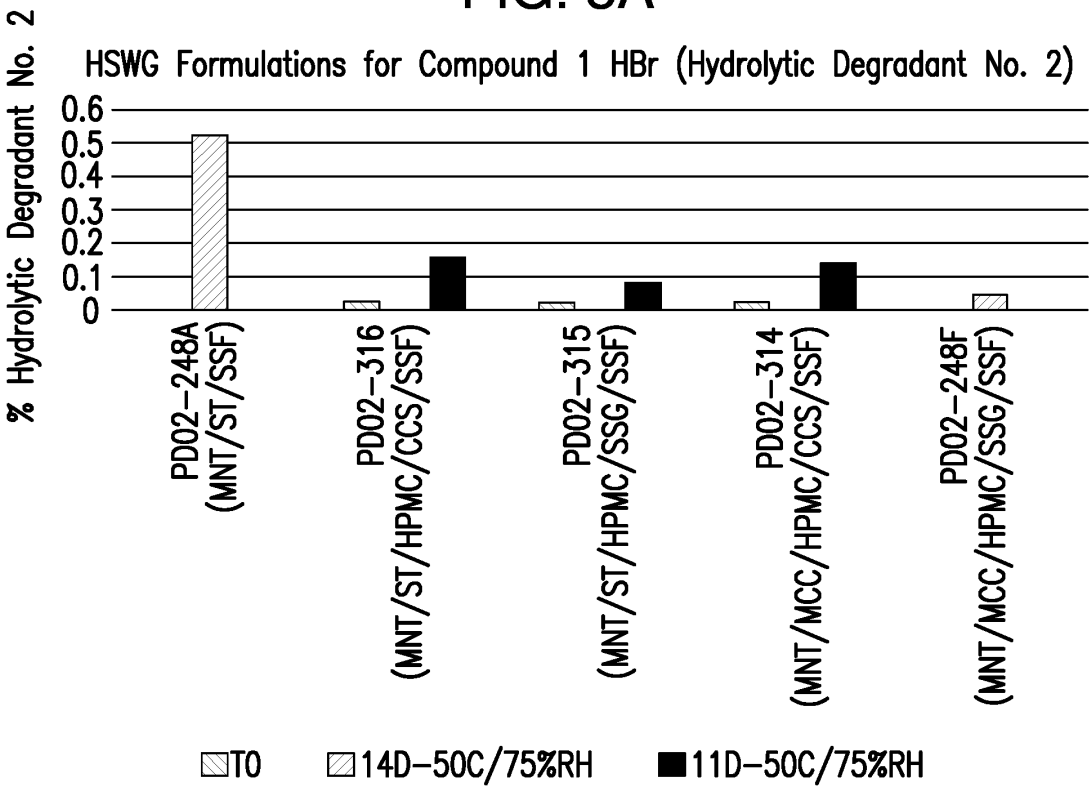

HSWG Formulations for Compound 1 HBr (Hydrolytic Degradant No. 2)
% Hydrolytic Degradant No. 2
0.6
0.5
0.4
0.3
0.2
0.1
0
PD02-248A (MNT/ST/SSF)
PD02-316 (MNT/ST/HPMC/CCS/SSF)
PD02-315 (MNT/ST/HPMC/SSG/SSF)
PD02-314 (MNT/MCC/HPMC/CCS/SSF)
PD02-248F (MNT/MCC/HPMC/SSG/SSF)
T0
14D-50C/75%RH
11D-50C/75%RH

FIG. 5B

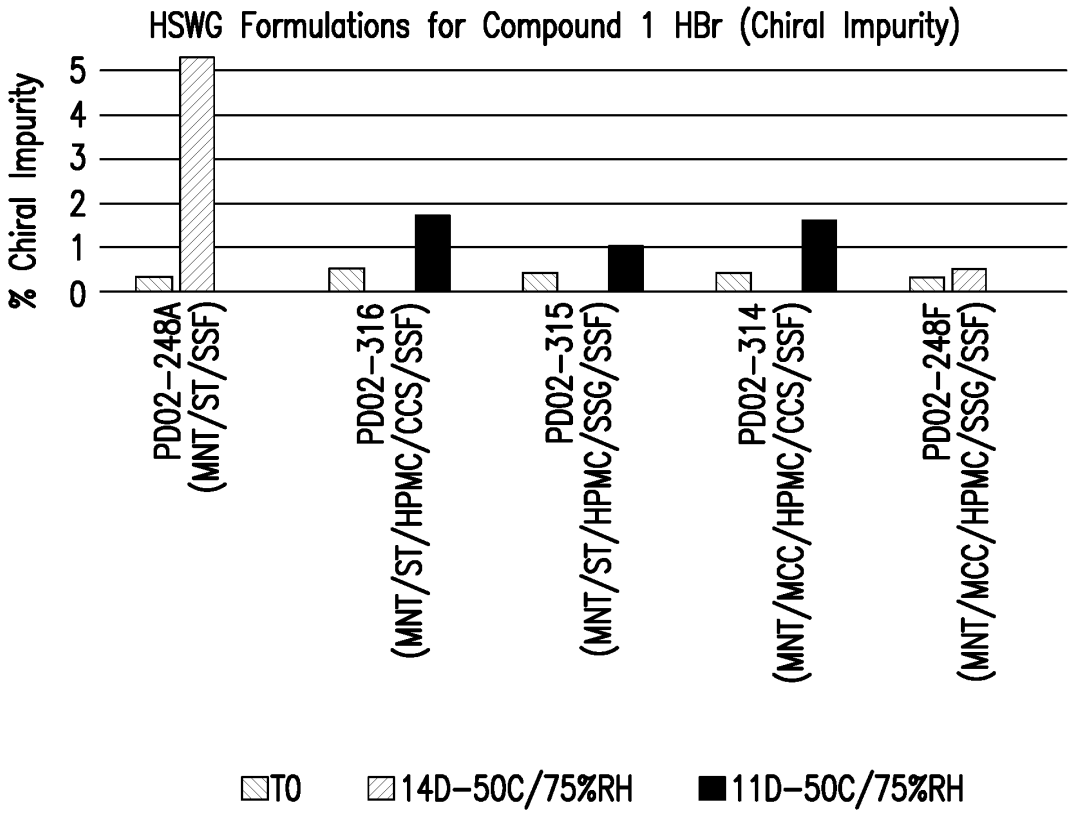

HSWG Formulations for Compound 1 HBr (Chiral Impurity)
% Chiral Impurity
5
4
3
2
1
0
PD02-248A (MNT/ST/SSF)
PD02-316 (MNT/ST/HPMC/CCS/SSF)
PD02-315 (MNT/ST/HPMC/SSG/SSF)
PD02-314 (MNT/MCC/HPMC/CCS/SSF)
PD02-248F (MNT/MCC/HPMC/SSG/SSF)
T0
14D-50C/75%RH
11D-50C/75%RH

FIG. 5C

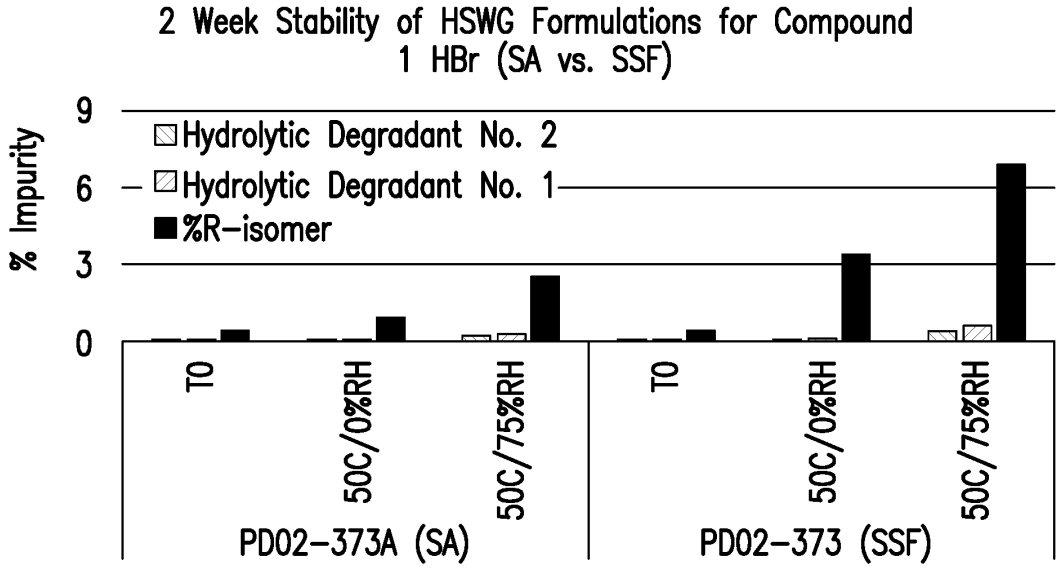

2 Week Stability of HSWG Formulations for Compound 1 HBr (SA vs. SSF)
% Impurity
9
6
3
0
Hydrolytic Degradant No. 2
Hydrolytic Degradant No. 1
%R-isomer
T0
50C/0%RH
50C/75%RH
T0
50C/0%RH
50C/75%RH
PD02-373A (SA)
PD02-373 (SSF)

FIG. 6A

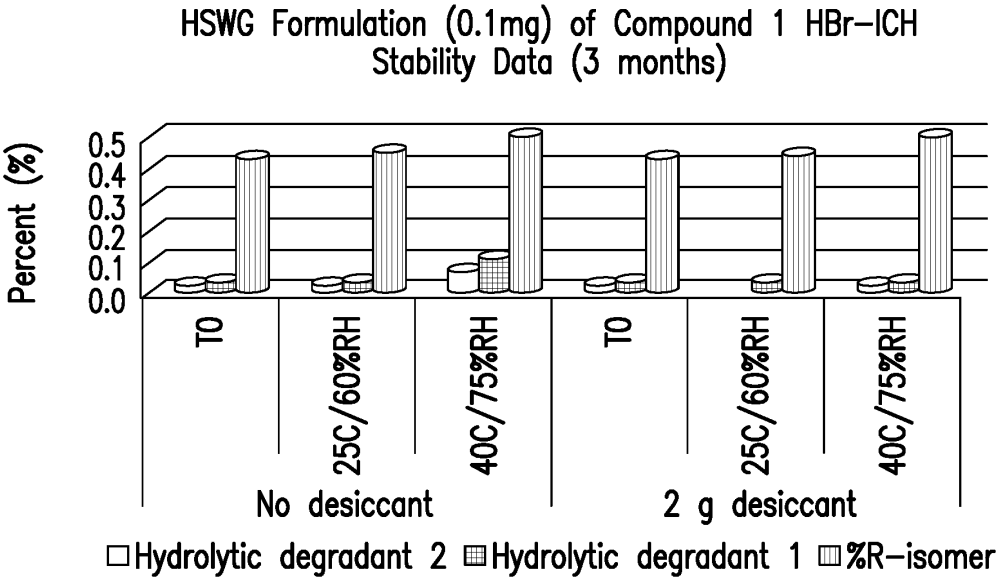

HSWG Formulation (0.1mg) of Compound 1 HBr-ICH Stability Data (3 months)
Percent (%)
0.5
0.4
0.3
0.2
0.1
0.0
T0
25C/60%RH
40C/75%RH
T0
25C/60%RH
40C/75%RH
No desiccant
2 g desiccant
Hydrolytic degradant 2
Hydrolytic degradant 1
%R-isomer

FIG. 6B

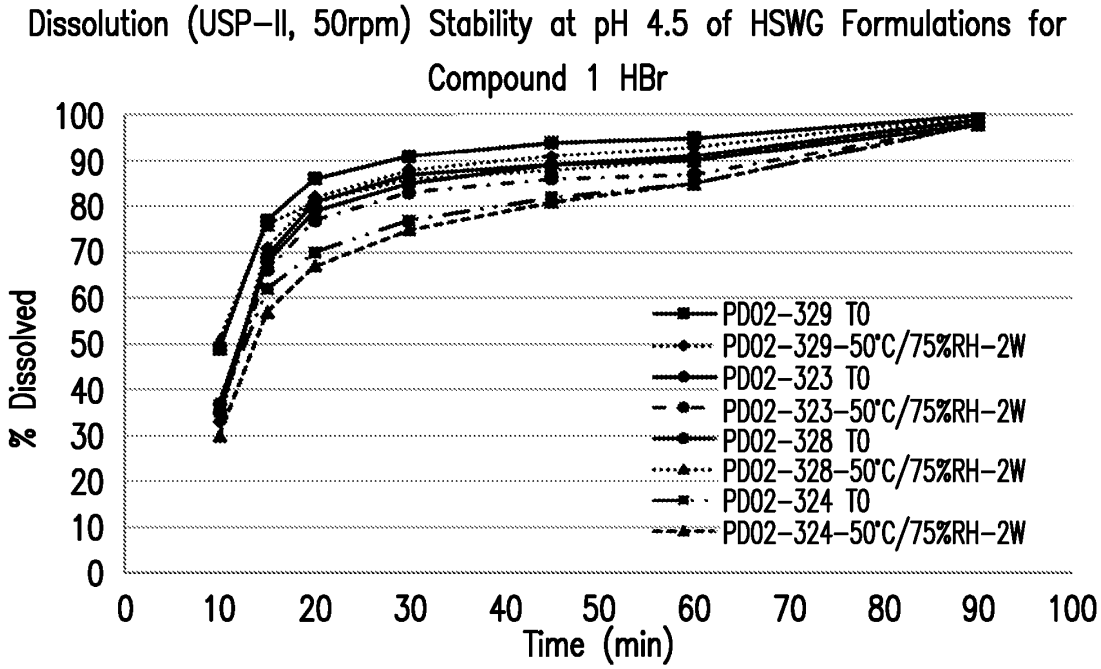

Dissolution (USP–II, 50rpm) Stability at pH 4.5 of HSWG Formulations for Compound 1 HBr
% Dissolved
Time (min)
PD02–329 T0
PD02–329–50°C/75%RH–2W
PD02–323 T0
PD02–323–50°C/75%RH–2W
PD02–328 T0
PD02–328–50°C/75%RH–2W
PD02–324 T0
PD02–324–50°C/75%RH–2W

FIG. 7

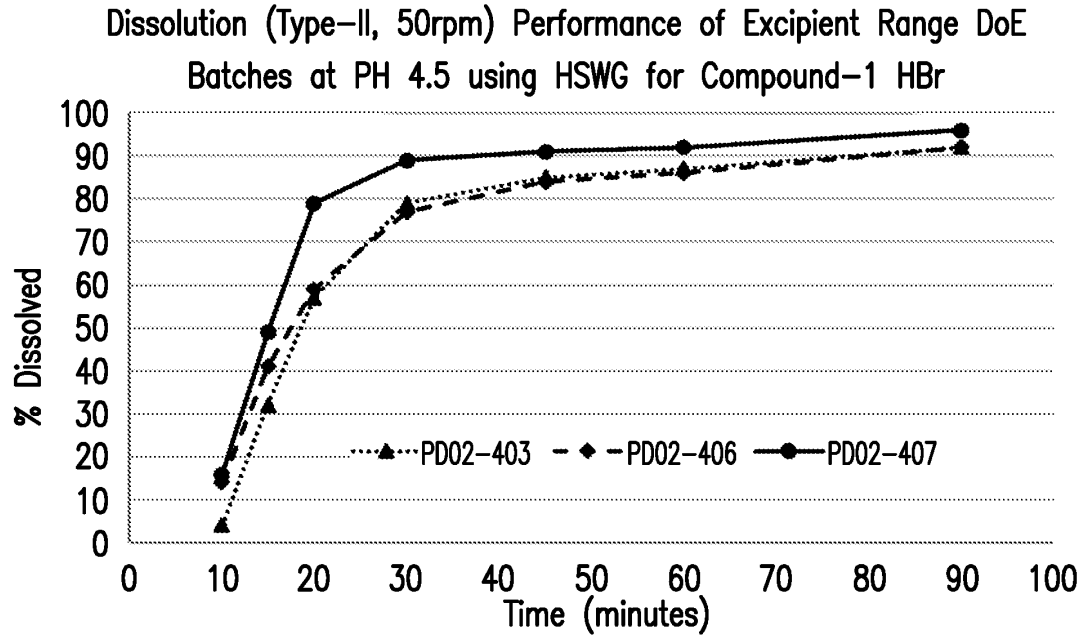

Dissolution (Type–II, 50rpm) Performance of Excipient Range DoE Batches at PH 4.5 using HSWG for Compound–1 HBr
% Dissolved
Time (minutes)
PD02–403
PD02–406
PD02–407

FIG. 8

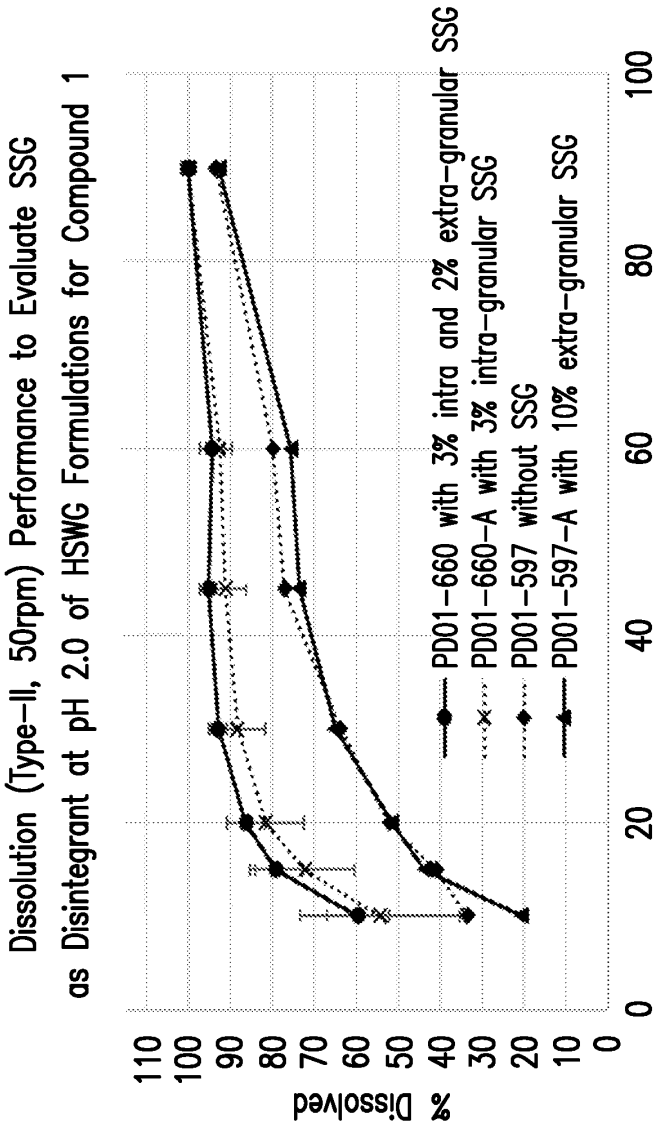

Dissolution (Type–II, 50rpm) Performance to Evaluate SSG
as Disintegrant at pH 2.0 of HSWG Formulations for Compound 1
% Dissolved
0
10
20
30
40
50
60
70
80
90
100
110
0
20
40
60
80
100
Time (Minutes)
PD01–660 with 3% intra and 2% extra–granular SSG
PD01–660–A with 3% intra–granular SSG
PD01–597 without SSG
PD01–597–A with 10% extra–granular SSG

FIG. 9

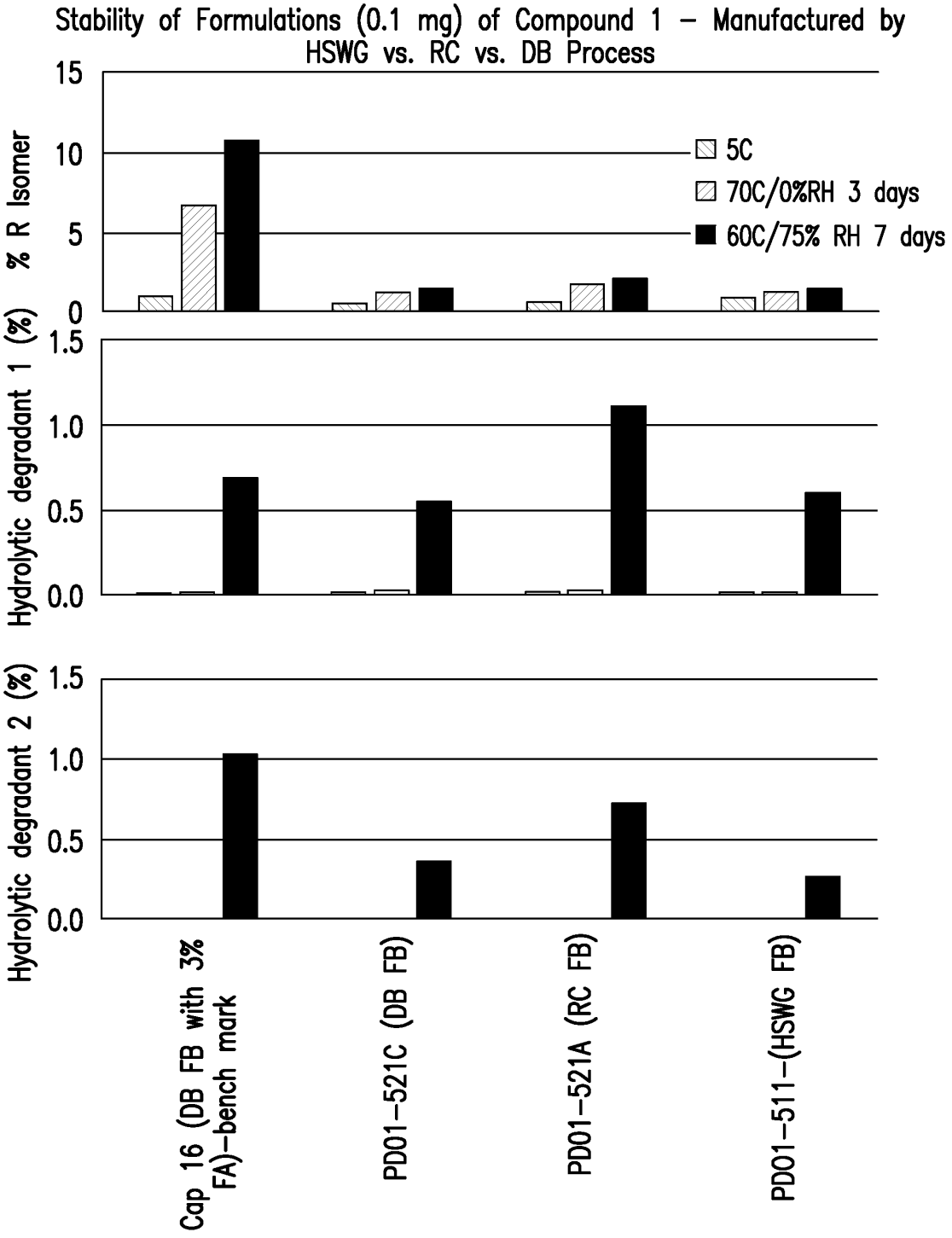

Stability of Formulations (0.1 mg) of Compound 1 – Manufactured by HSWG vs. RC vs. DB Process
% R Isomer
Hydrolytic degradant 1 (%)
Hydrolytic degradant 2 (%)
5C
70C/0%RH 3 days
60C/75% RH 7 days
Cap 16 (DB FB with 3% FA)–bench mark
PD01–521C (DB FB)
PD01–521A (RC FB)
PD01–511–(HSWG FB)

FIG. 10A

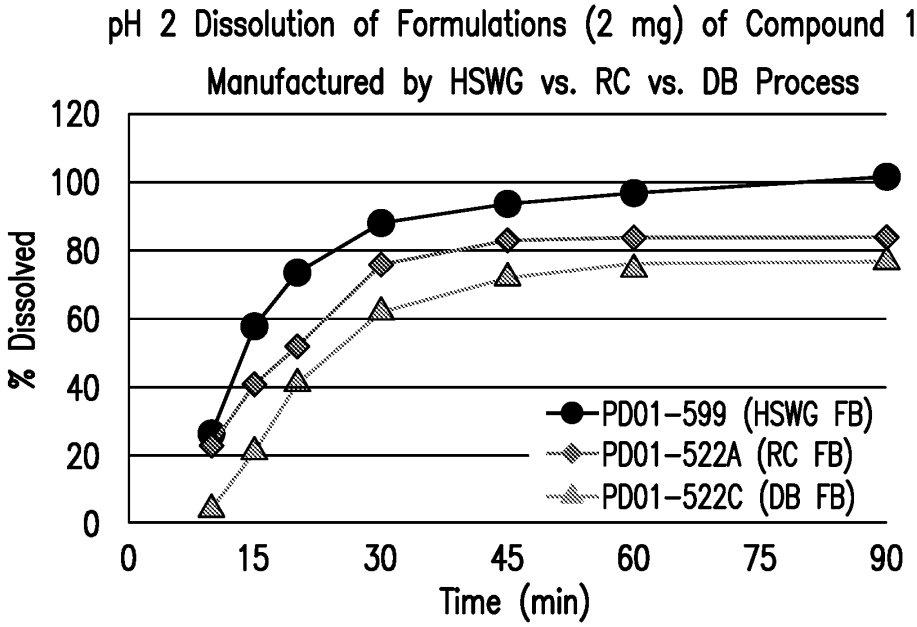


FIG. 10B

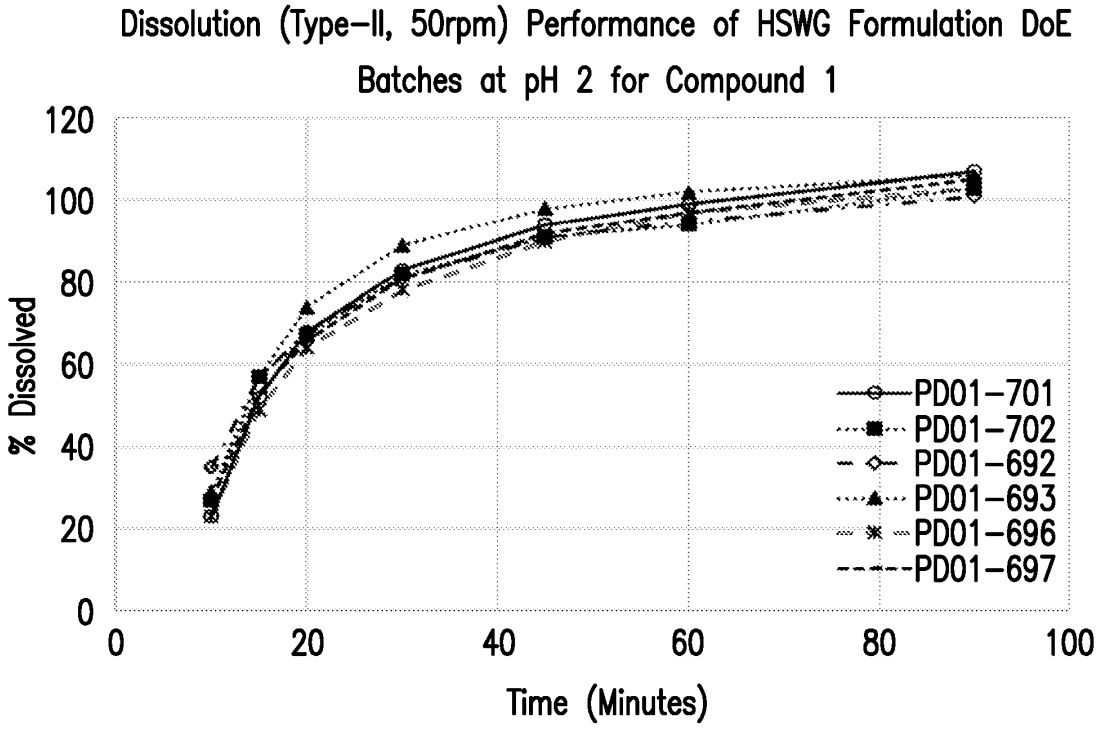


FIG. 11

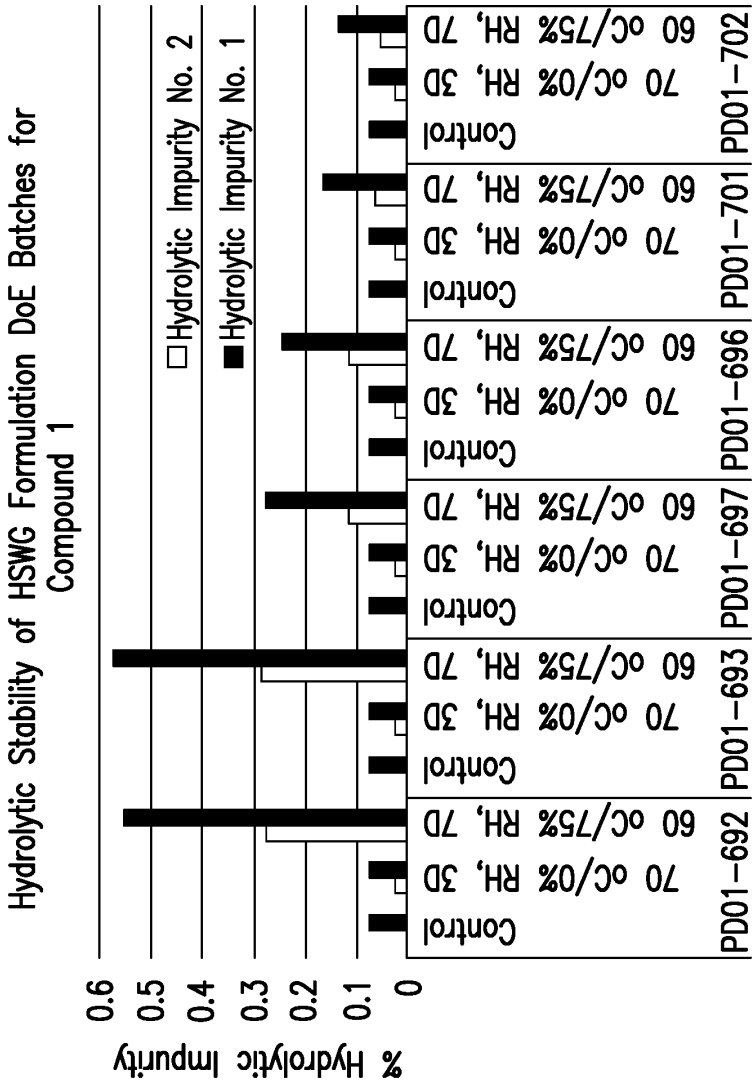

Hydrolytic Stability of HSWG Formulation DoE Batches for Compound 1
□Hydrolytic Impurity No. 2
■Hydrolytic Impurity No. 1
% Hydrolytic Impurity
0
0.1
0.2
0.3
0.4
0.5
0.6
PD01-692
PD01-693
PD01-697
PD01-696
PD01-701
PD01-702
Control
70 oC/0% RH, 3D
60 oC/75% RH, 7D

FIG. 12A

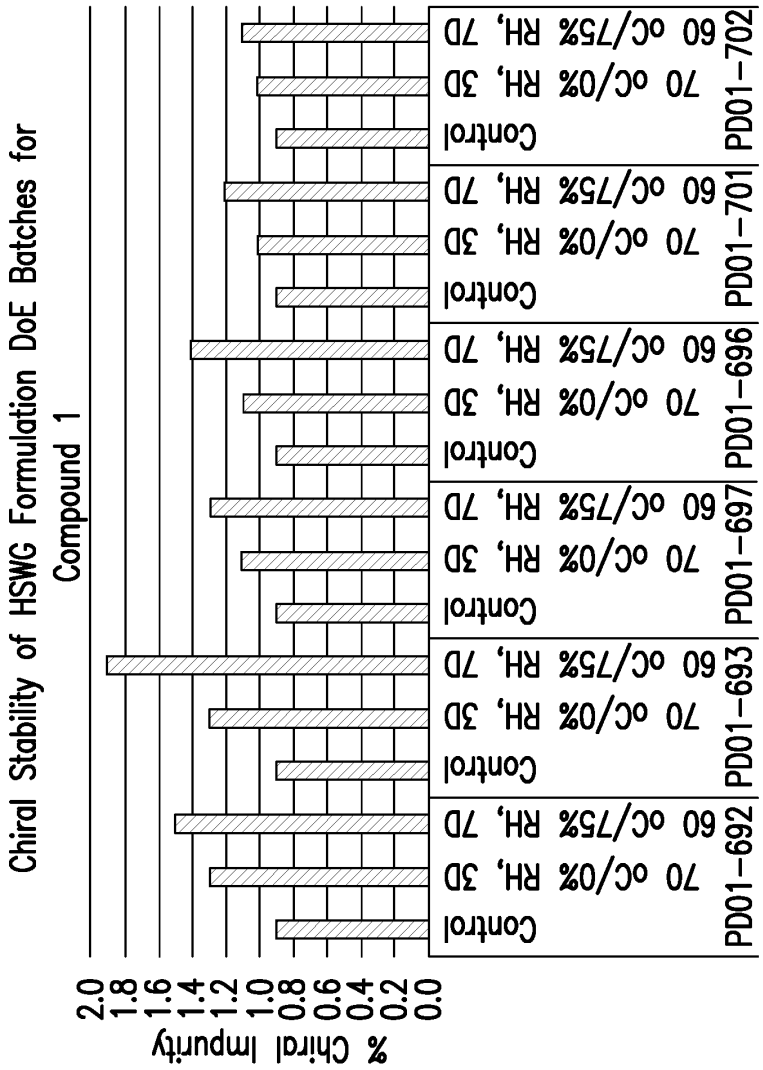

Chiral Stability of HSWG Formulation DoE Batches for Compound 1
% Chiral Impurity
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
PD01-692
PD01-693
PD01-697
PD01-696
PD01-701
PD01-702
Control
70 oC/0% RH, 3D
60 oC/75% RH, 7D

FIG. 12B

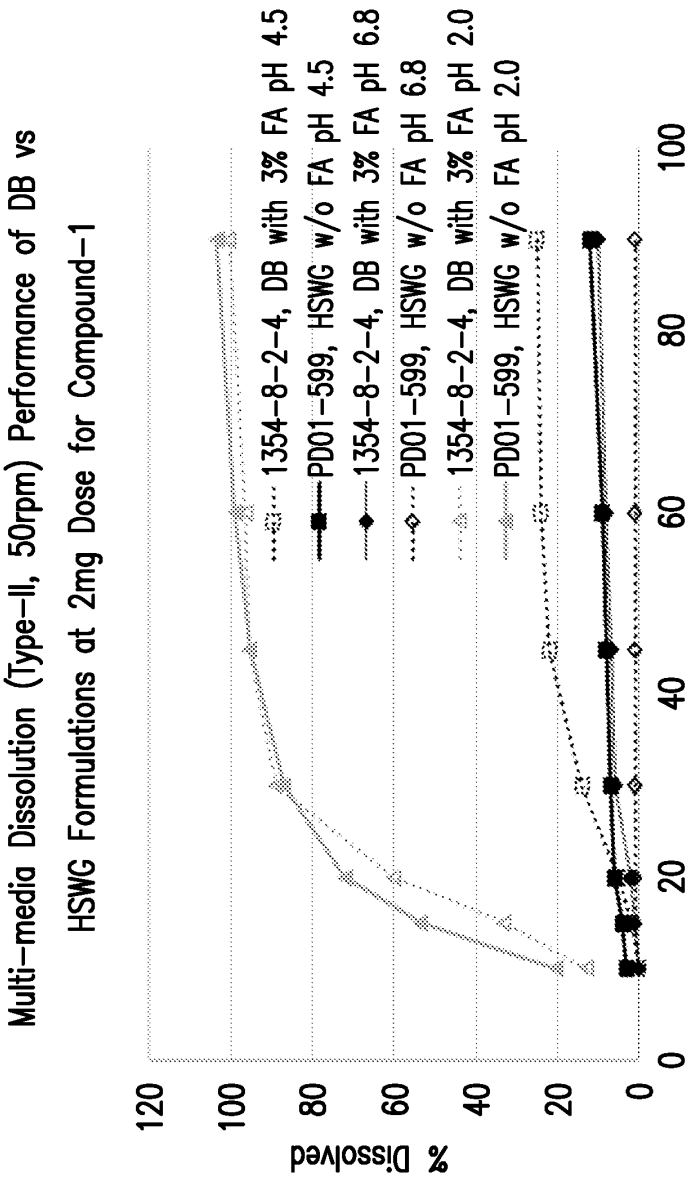

Multi-media Dissolution (Type-II, 50rpm) Performance of DB vs
HSWG Formulations at 2mg Dose for Compound-1
1354-8-2-4, DB with 3% FA pH 4.5
PD01-599, HSWG w/o FA pH 4.5
1354-8-2-4, DB with 3% FA pH 6.8
PD01-599, HSWG w/o FA pH 6.8
1354-8-2-4, DB with 3% FA pH 2.0
PD01-599, HSWG w/o FA pH 2.0
% Dissolved
120
100
80
60
40
20
0
0
20
40
60
80
100
Time (Minutes)

FIG. 13

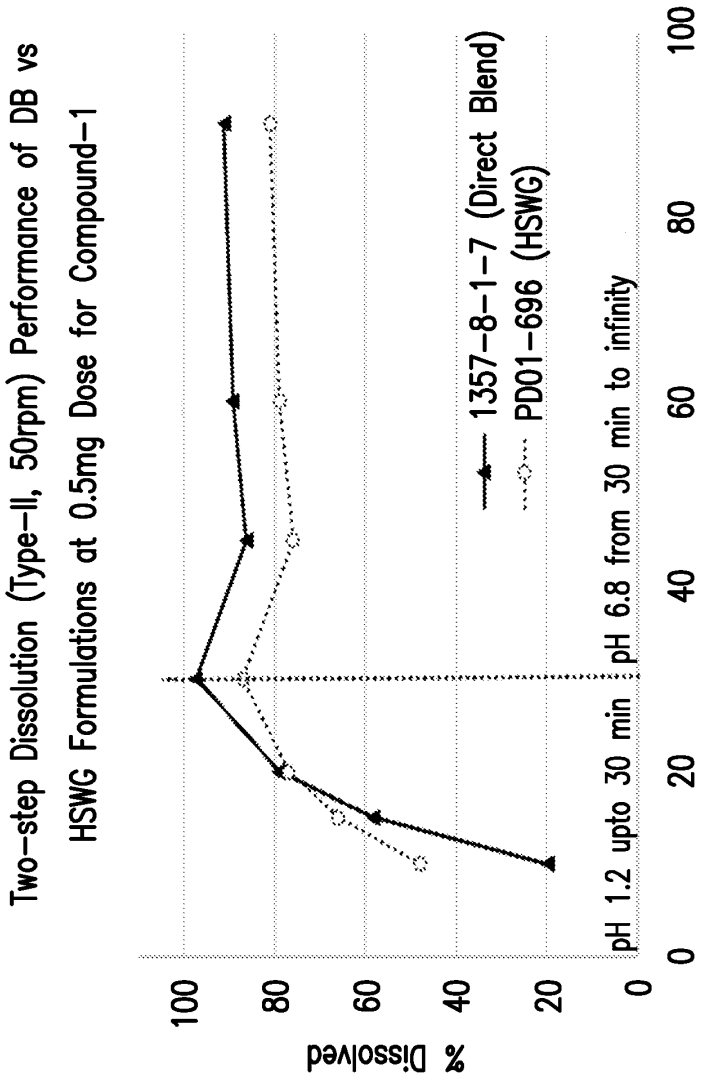

Two-step Dissolution (Type-II, 50rpm) Performance of DB vs
HSWG Formulations at 0.5mg Dose for Compound-1
% Dissolved
100
80
60
40
20
0
0
20
40
60
80
100
Time (Minutes)
pH 1.2 upto 30 min
pH 6.8 from 30 min to infinity
1357-8-1-7 (Direct Blend)
PD01-696 (HSWG)

FIG. 14

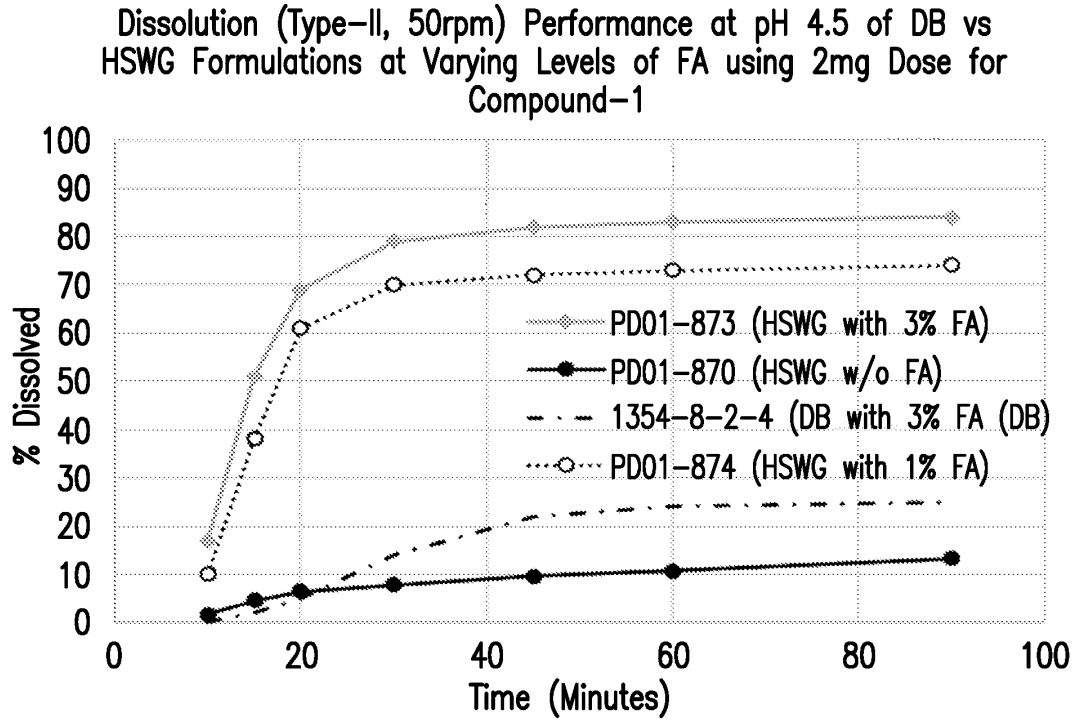

Dissolution (Type–II, 50rpm) Performance at pH 4.5 of DB vs HSWG Formulations at Varying Levels of FA using 2mg Dose for Compound–1
% Dissolved
Time (Minutes)
PD01–873 (HSWG with 3% FA)
PD01–870 (HSWG w/o FA)
1354–8–2–4 (DB with 3% FA (DB)
PD01–874 (HSWG with 1% FA)

FIG. 15

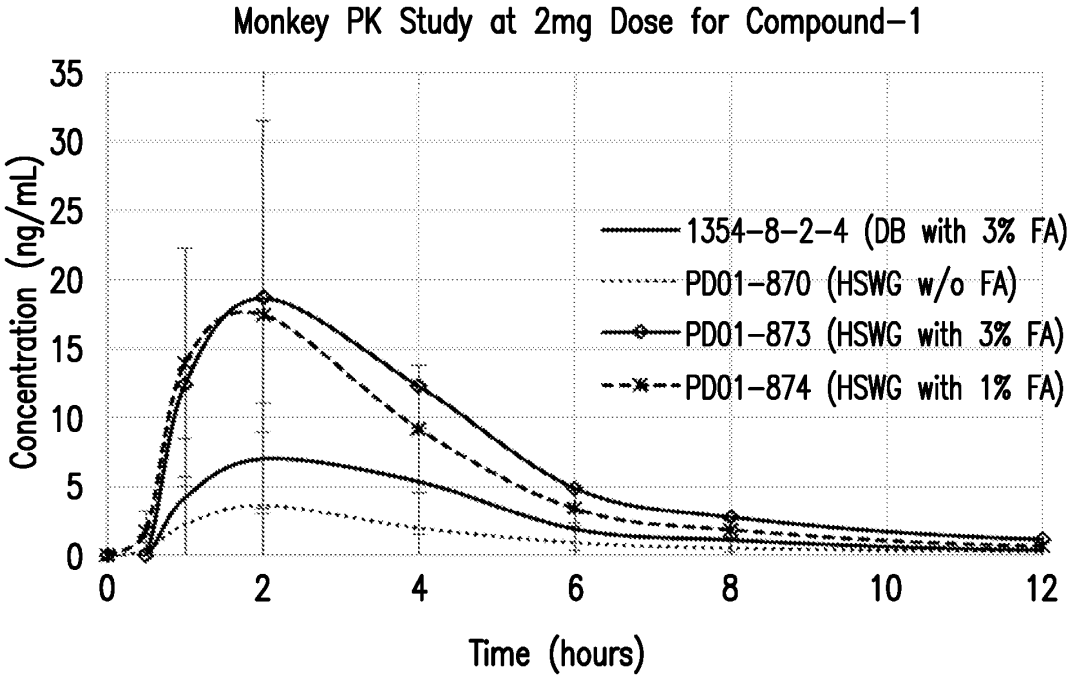

Monkey PK Study at 2mg Dose for Compound–1
Concentration (ng/mL)
Time (hours)
1354–8–2–4 (DB with 3% FA)
PD01–870 (HSWG w/o FA)
PD01–873 (HSWG with 3% FA)
PD01–874 (HSWG with 1% FA)

FIG. 16

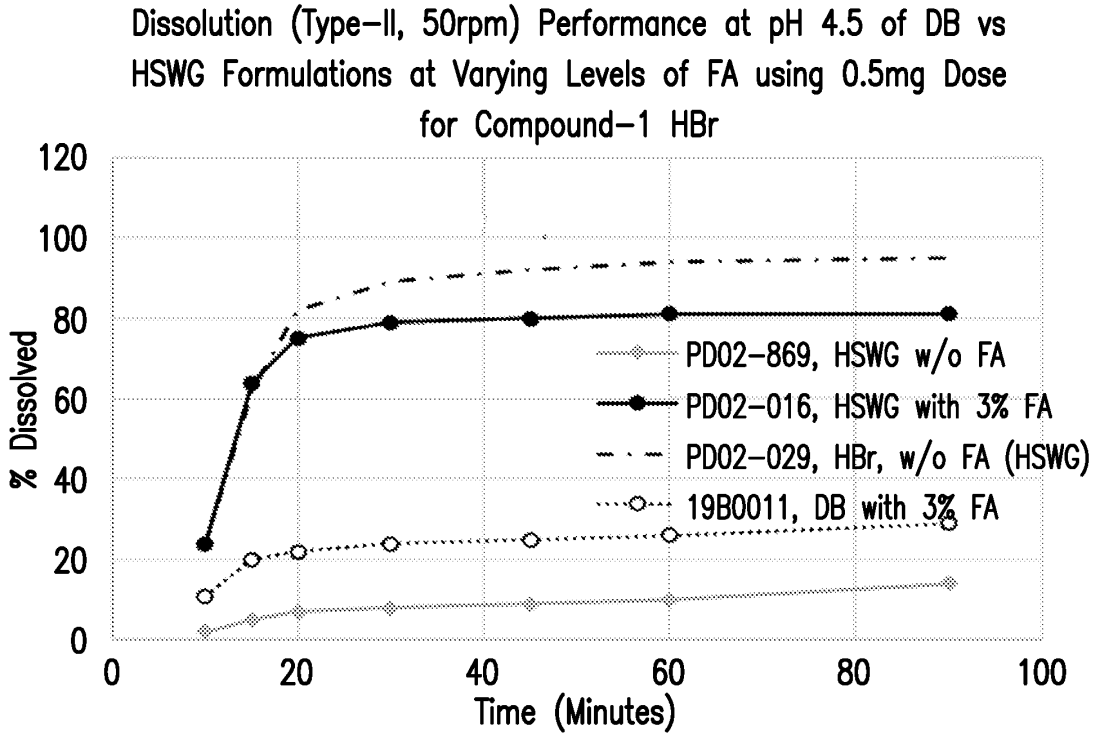

Dissolution (Type–II, 50rpm) Performance at pH 4.5 of DB vs HSWG Formulations at Varying Levels of FA using 0.5mg Dose for Compound–1 HBr
% Dissolved
Time (Minutes)
PD02–869, HSWG w/o FA
PD02–016, HSWG with 3% FA
PD02–029, HBr, w/o FA (HSWG)
19B0011, DB with 3% FA

FIG. 17

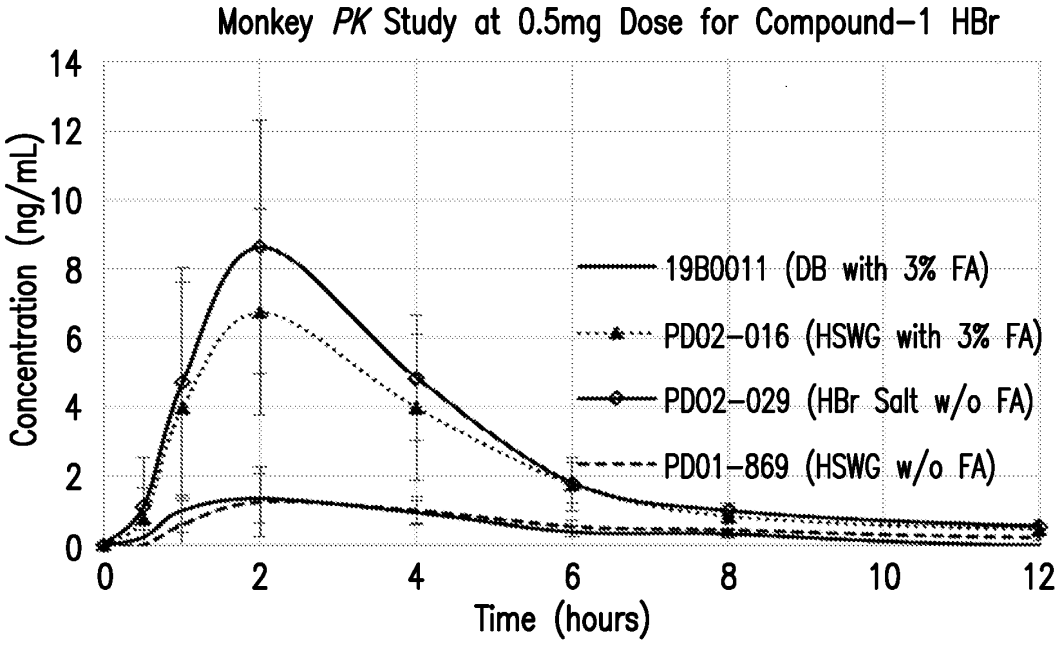

Monkey *PK* Study at 0.5mg Dose for Compound–1 HBr
Concentration (ng/mL)
Time (hours)
19B0011 (DB with 3% FA)
PD02–016 (HSWG with 3% FA)
PD02–029 (HBr Salt w/o FA)
PD01–869 (HSWG w/o FA)

FIG. 18

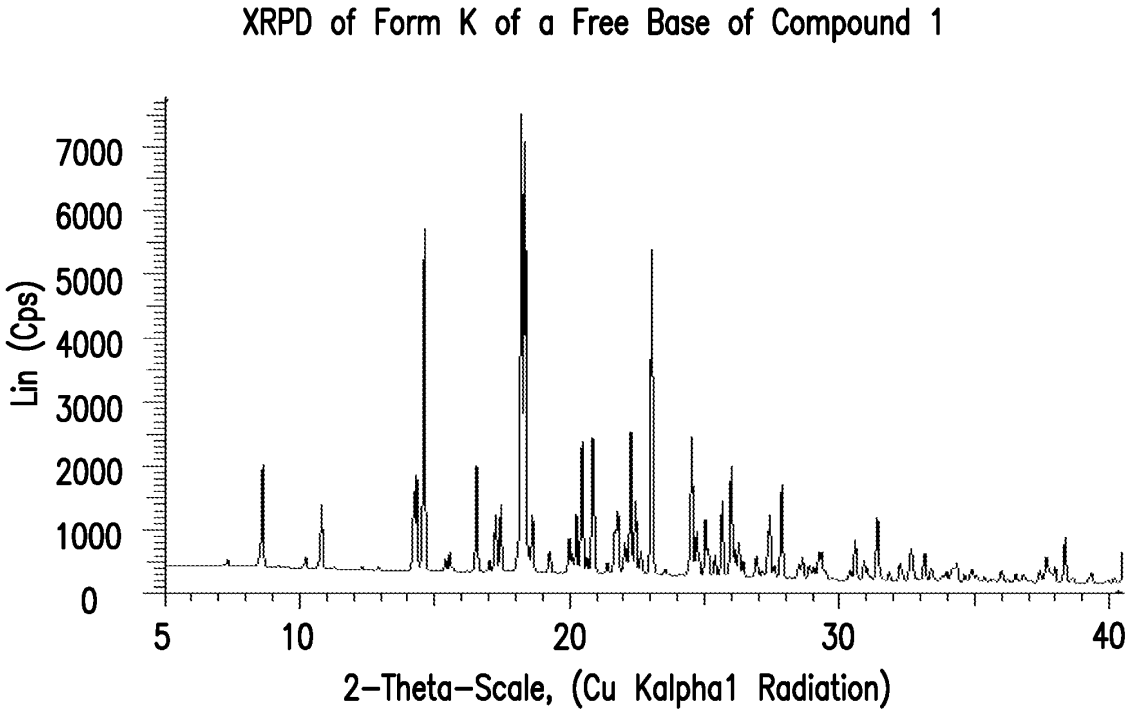

XRPD of Form K of a Free Base of Compound 1
Lin (Cps)
7000
6000
5000
4000
3000
2000
1000
0
5
10
20
30
40
2-Theta-Scale, (Cu Kalpha1 Radiation)

FIG. 19

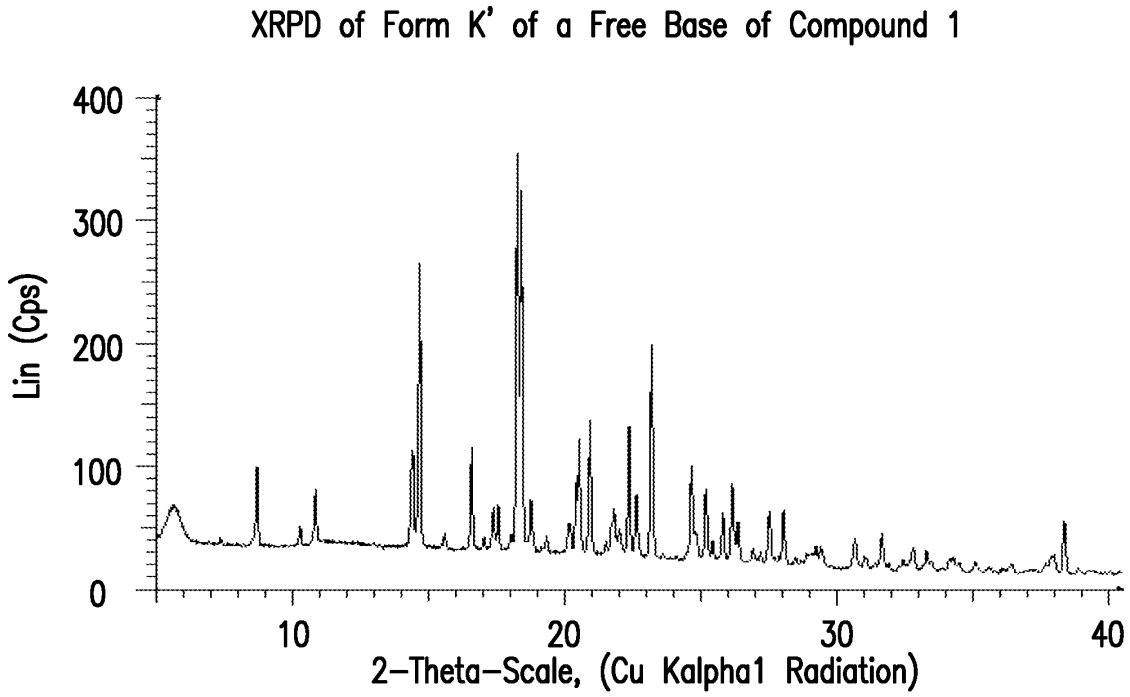

XRPD of Form K' of a Free Base of Compound 1
Lin (Cps)
400
300
200
100
0
10
20
30
40
2-Theta-Scale, (Cu Kalpha1 Radiation)

FIG. 20

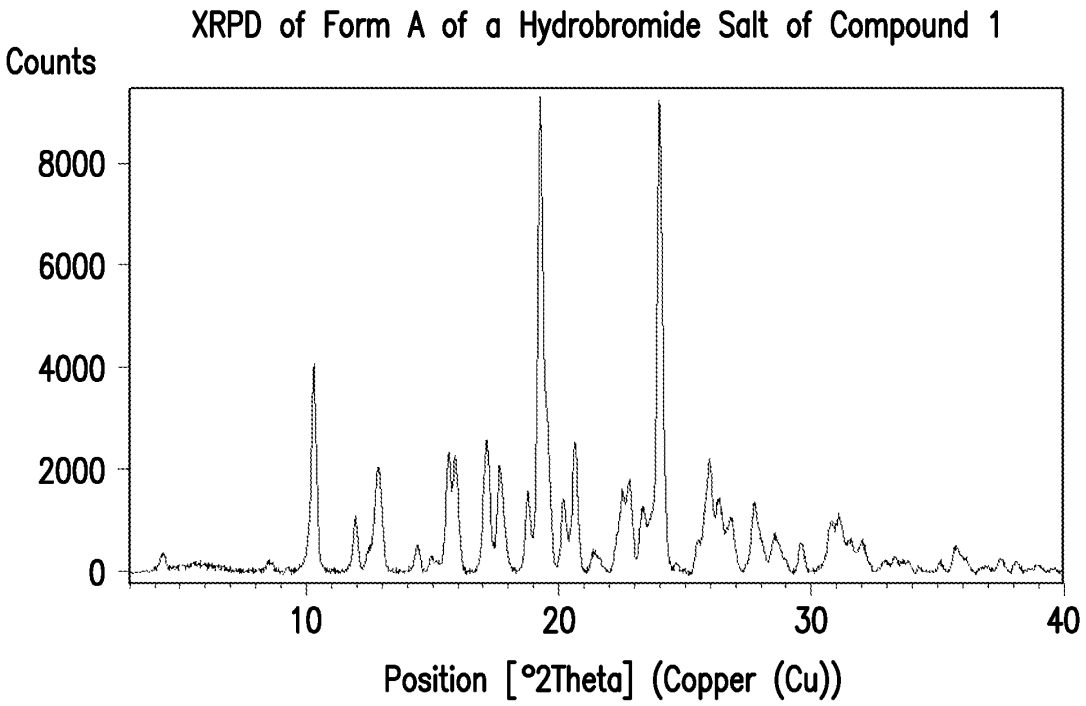

XRPD of Form A of a Hydrobromide Salt of Compound 1
Counts
8000
6000
4000
2000
0
10
20
30
40
Position [°2Theta] (Copper (Cu))

FIG. 21