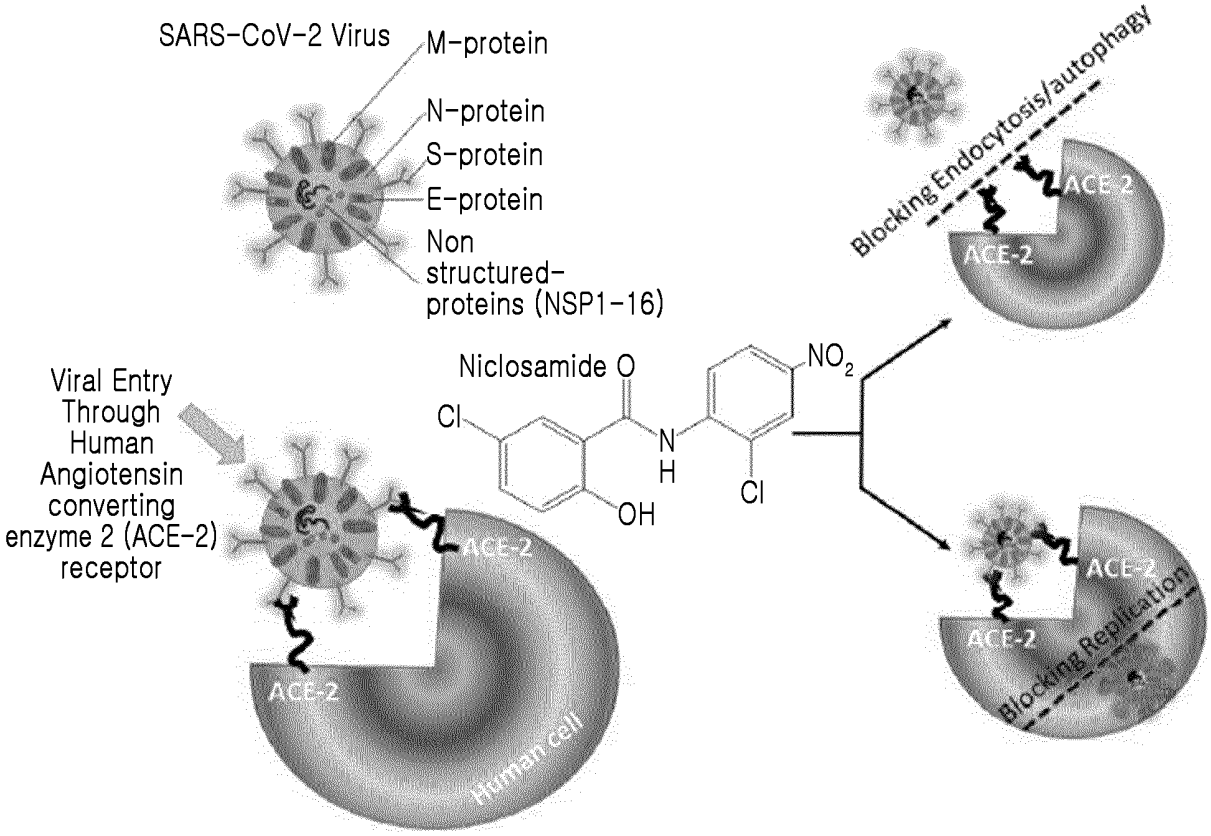

SARS-CoV-2 Virus
M-protein
N-protein
S-protein
E-protein
Non structured-proteins (NSP1-16)
Viral Entry Through Human Angiotensin converting enzyme 2 (ACE-2) receptor
ACE-2
ACE-2
Human cell
Niclosamide
O
Cl
N
H
OH
Cl
NO2
Blocking Endocytosis/autophagy
ACE-2
ACE-2
ACE-2
ACE-2
Blocking Replication

FIG. 1

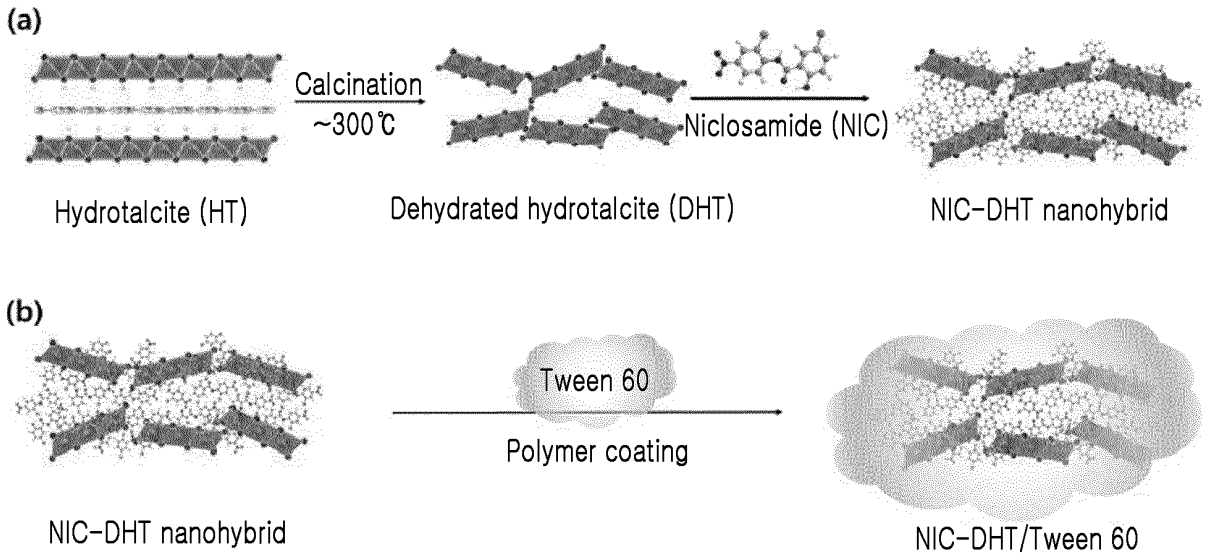

(a)
Calcination
~300℃
Niclosamide (NIC)
Hydrotalcite (HT)
Dehydrated hydrotalcite (DHT)
NIC-DHT nanohybrid
(b)
Tween 60
Polymer coating
NIC-DHT nanohybrid
NIC-DHT/Tween 60

FIG. 2

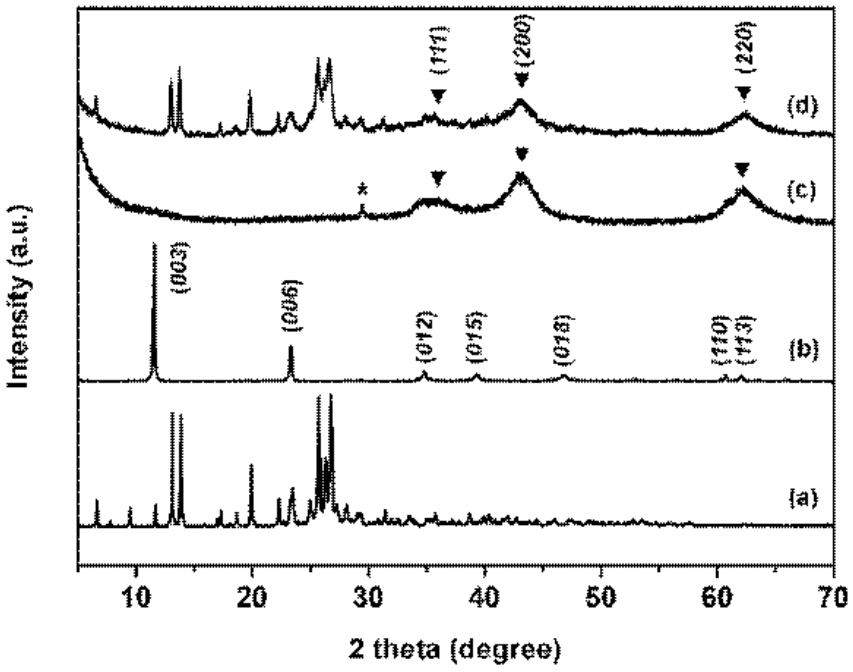

Intensity (a.u.)
(111)
(200)
(220)
(d)
(c)
*
(003)
(006)
(012)
(015)
(018)
(110)
(113)
(b)
(a)
10
20
30
40
50
60
70
2 theta (degree)

FIG. 3

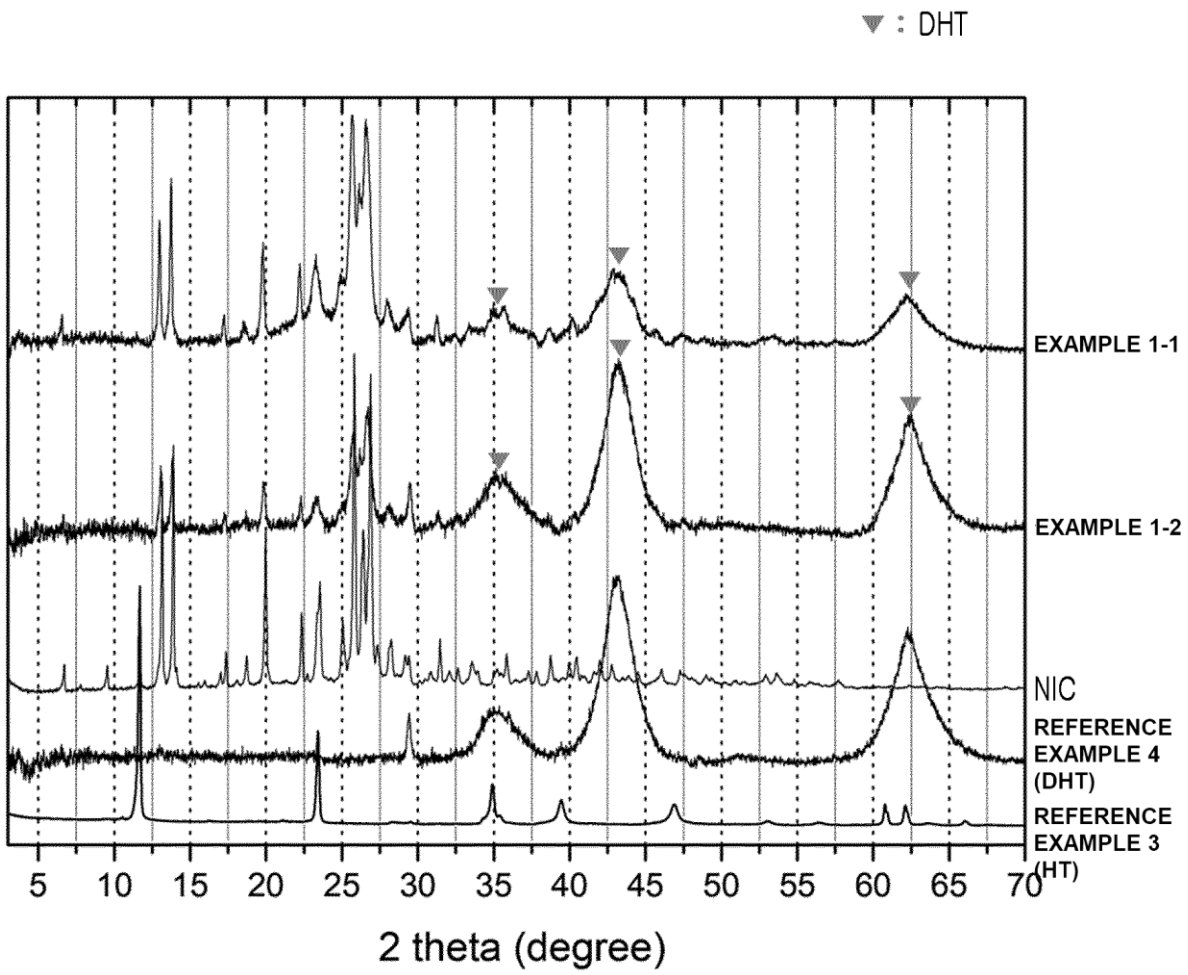

▼ : DHT
EXAMPLE 1-1
EXAMPLE 1-2
NIC
REFERENCE EXAMPLE 4 (DHT)
REFERENCE EXAMPLE 3 (HT)
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta (degree)

FIG. 4

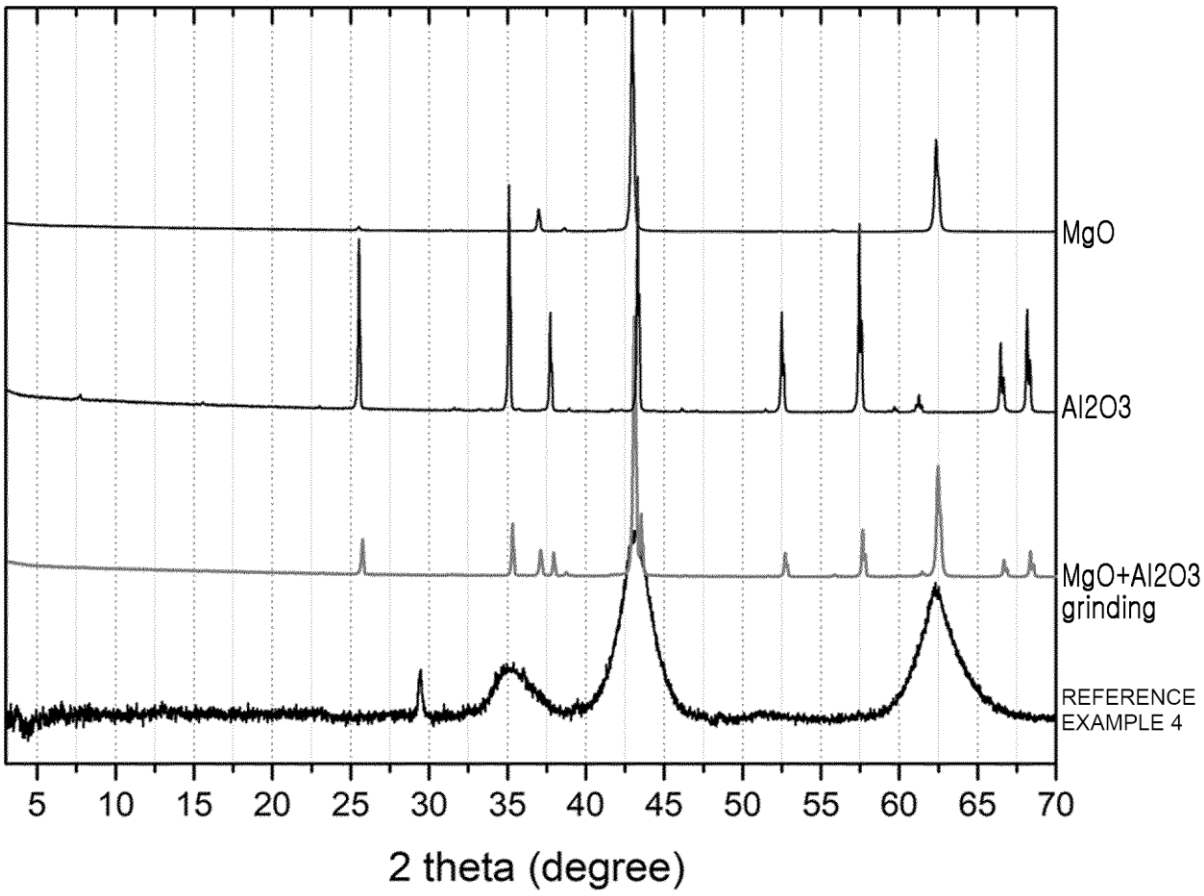

MgO
Al2O3
MgO+Al2O3
grinding
REFERENCE
EXAMPLE 4
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta (degree)

FIG. 5

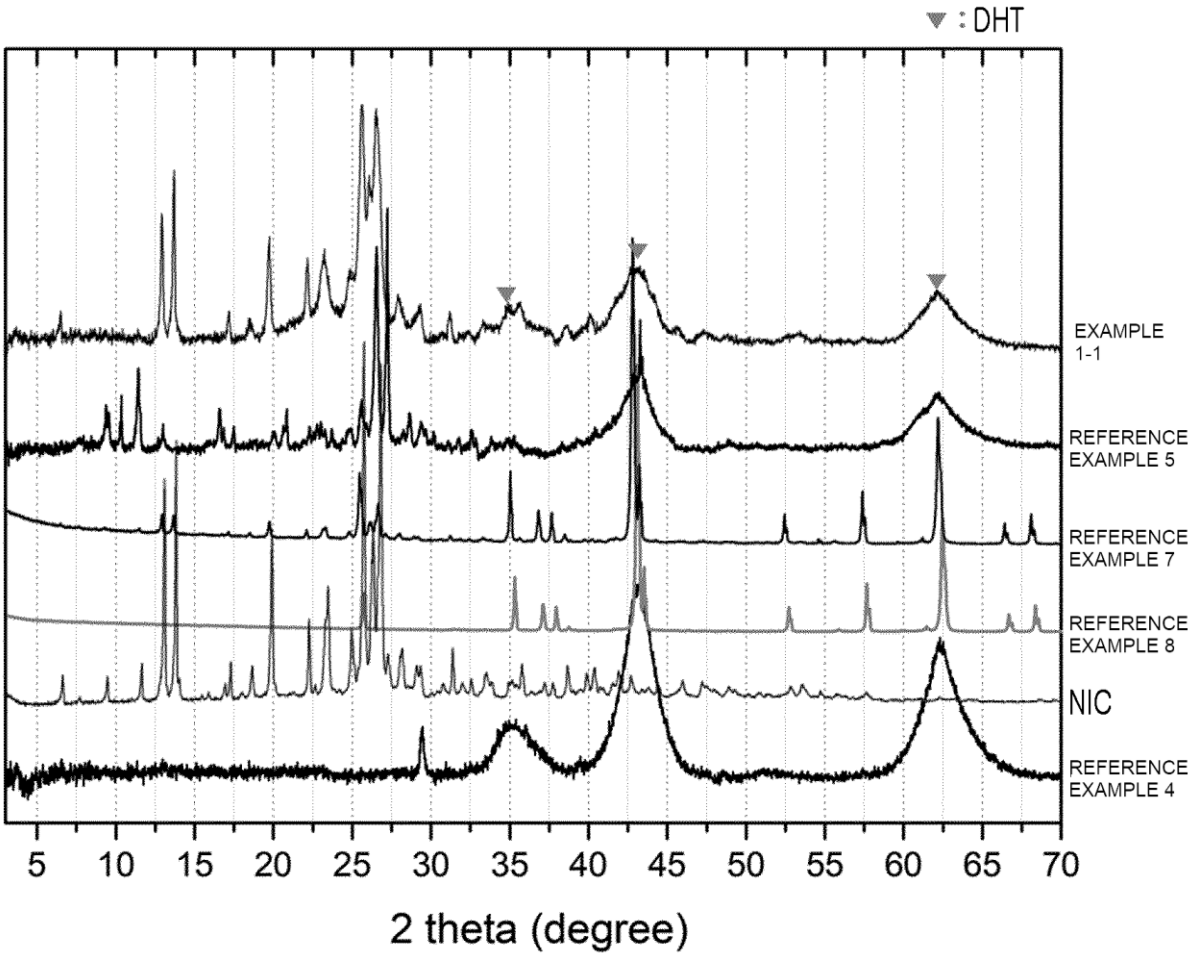

▼ : DHT
EXAMPLE 1-1
REFERENCE EXAMPLE 5
REFERENCE EXAMPLE 7
REFERENCE EXAMPLE 8
NIC
REFERENCE EXAMPLE 4
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta (degree)

FIG. 6

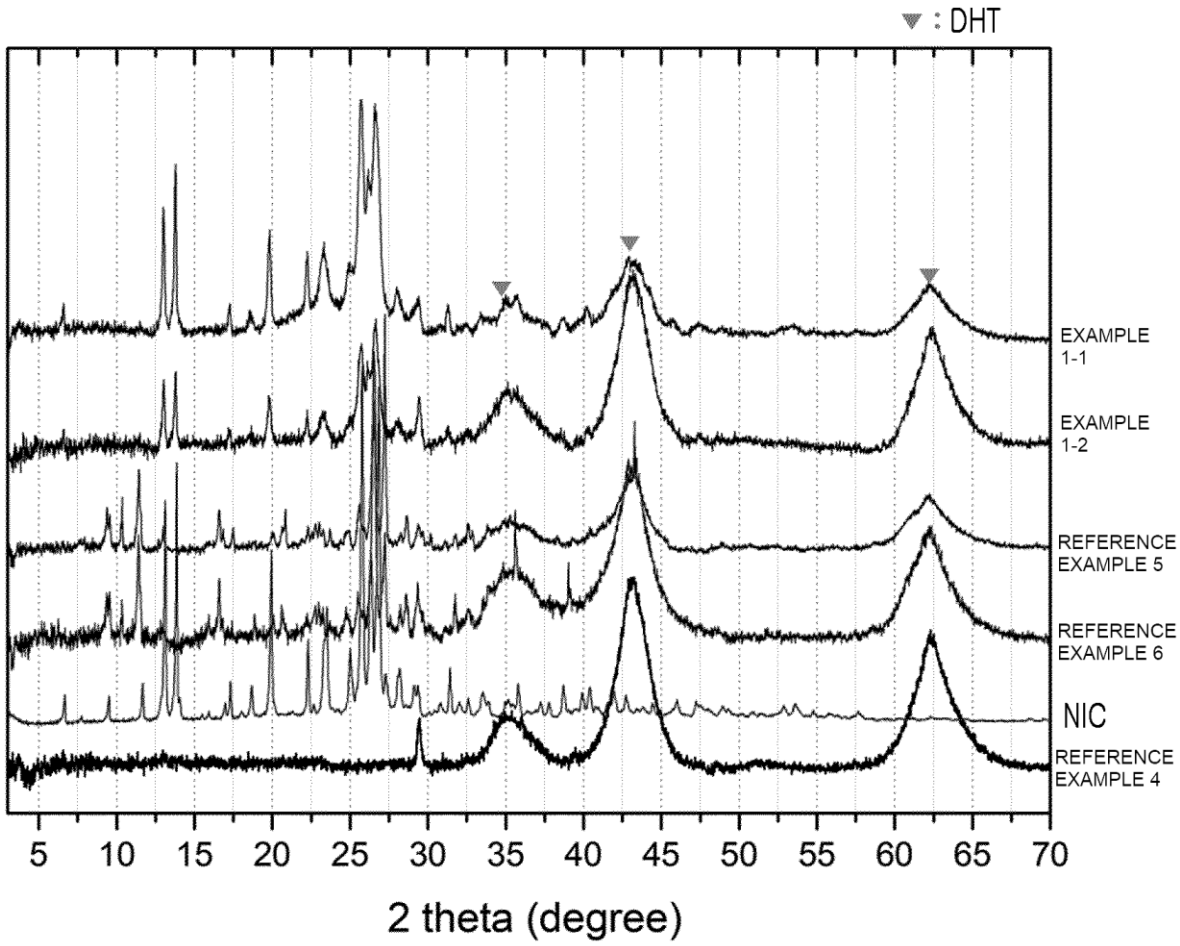

▼ : DHT
EXAMPLE 1-1
EXAMPLE 1-2
REFERENCE EXAMPLE 5
REFERENCE EXAMPLE 6
NIC
REFERENCE EXAMPLE 4
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta (degree)

FIG. 7

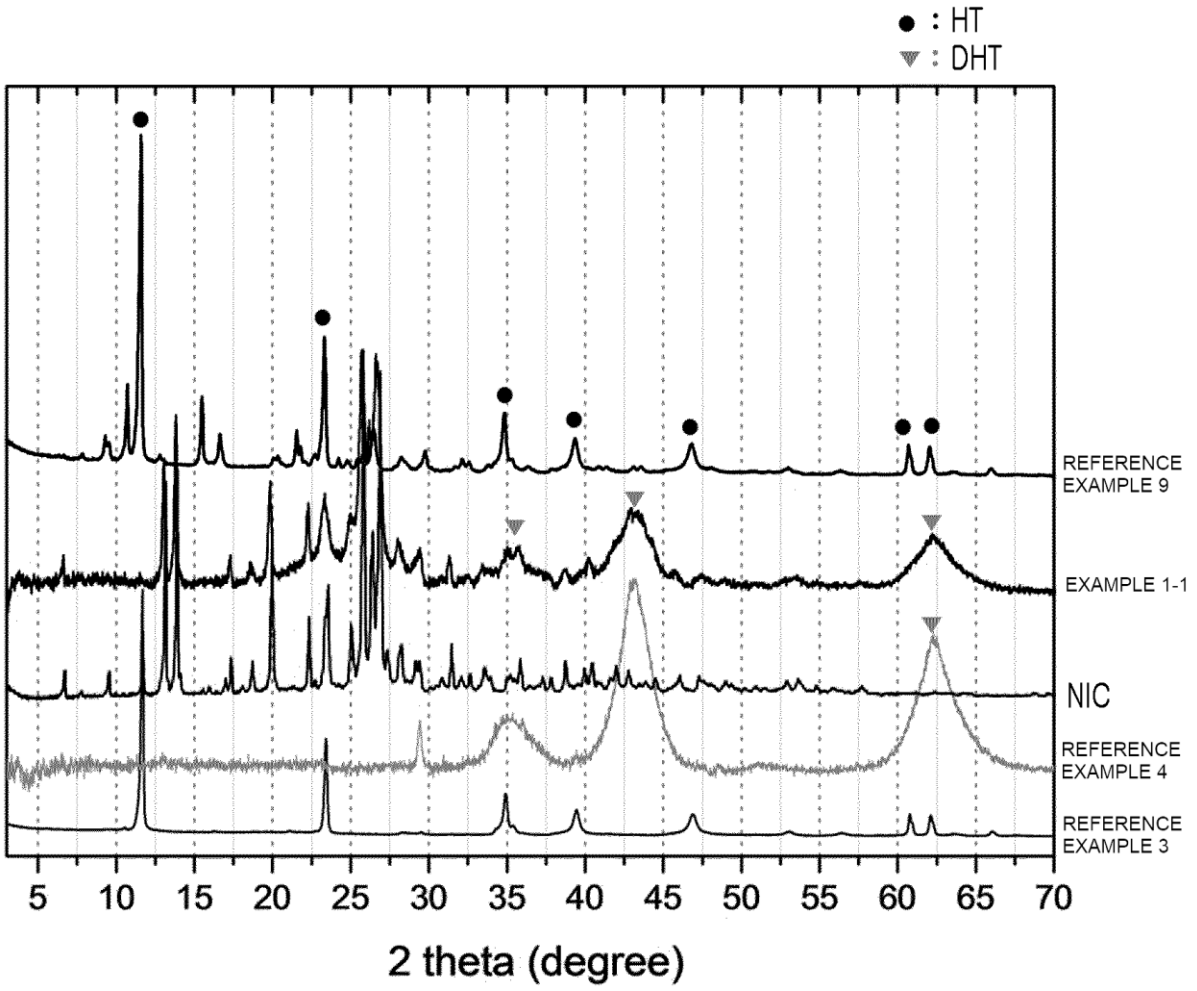

● : HT
▼ : DHT
REFERENCE EXAMPLE 9
EXAMPLE 1-1
NIC
REFERENCE EXAMPLE 4
REFERENCE EXAMPLE 3
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta (degree)

FIG. 8

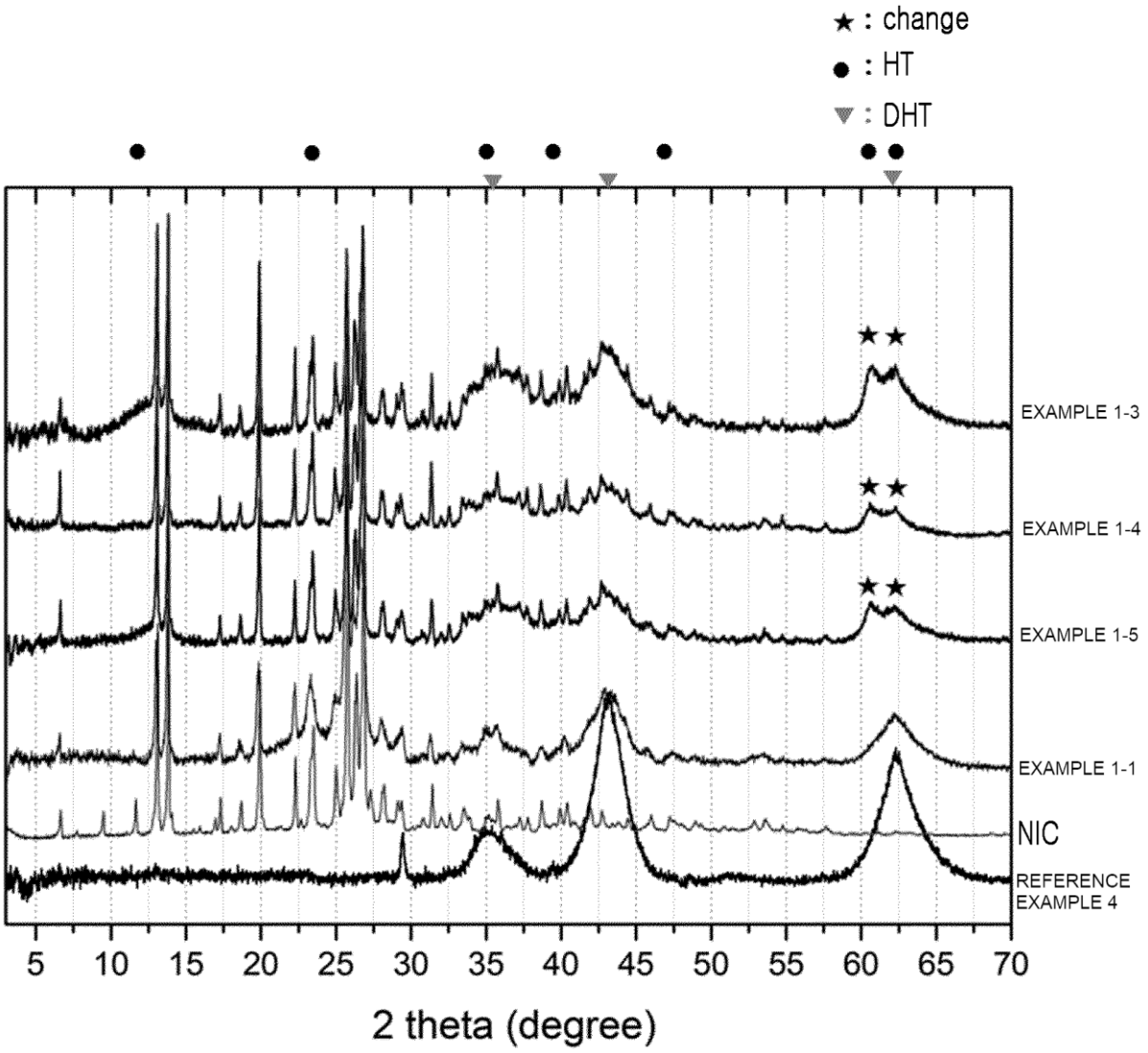

★ : change
● : HT
▼ : DHT
EXAMPLE 1-3
EXAMPLE 1-4
EXAMPLE 1-5
EXAMPLE 1-1
NIC
REFERENCE EXAMPLE 4
5 10 15 20 25 30 35 40 45 50 55 60 65 70
2 theta (degree)

FIG. 9

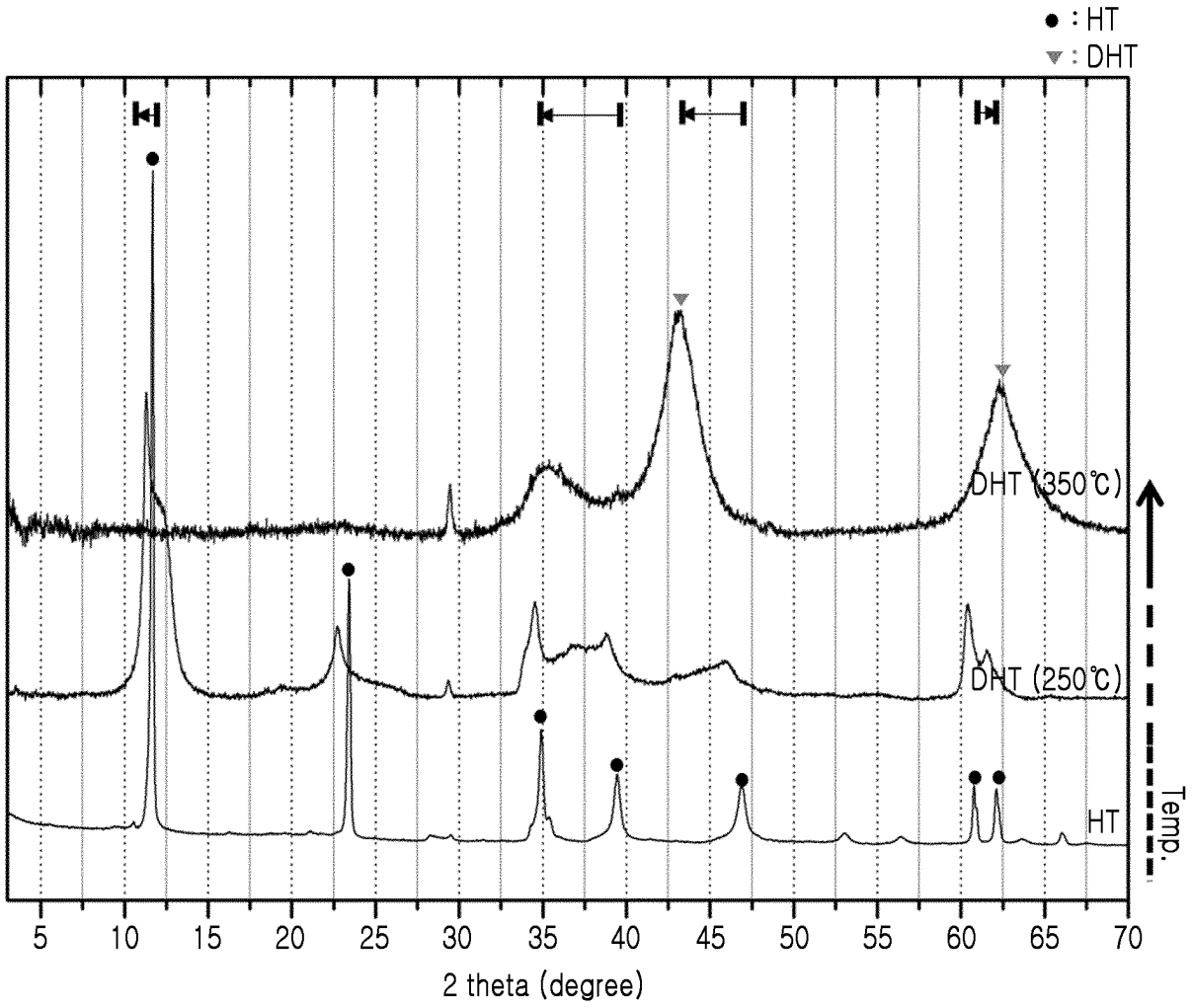

● : HT
▼ : DHT
DHT (350℃)
DHT (250℃)
HT
Temp.
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta (degree)

FIG. 10

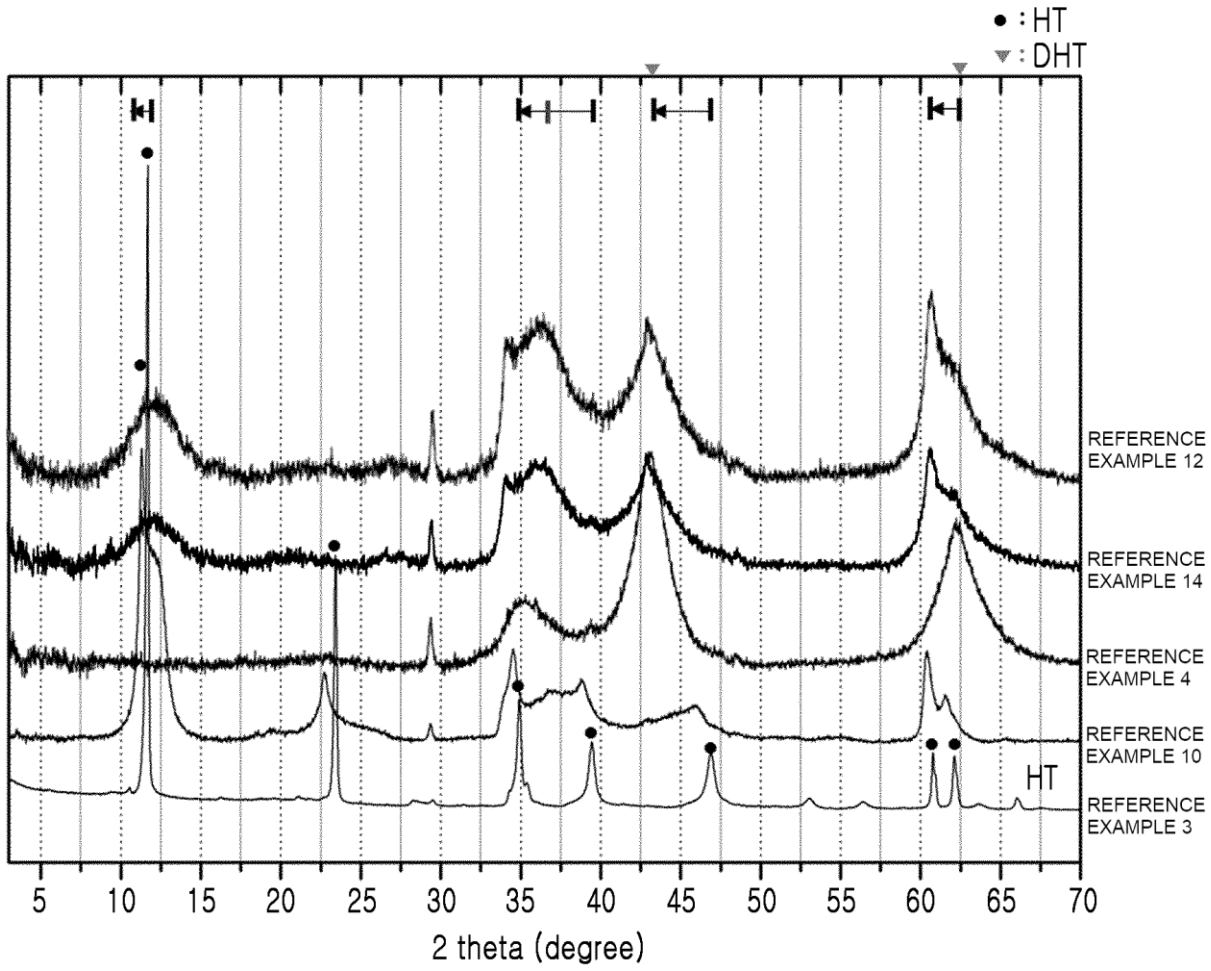

● : HT
▼ : DHT
REFERENCE EXAMPLE 12
REFERENCE EXAMPLE 14
REFERENCE EXAMPLE 4
REFERENCE EXAMPLE 10
HT
REFERENCE EXAMPLE 3
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta (degree)

FIG. 11

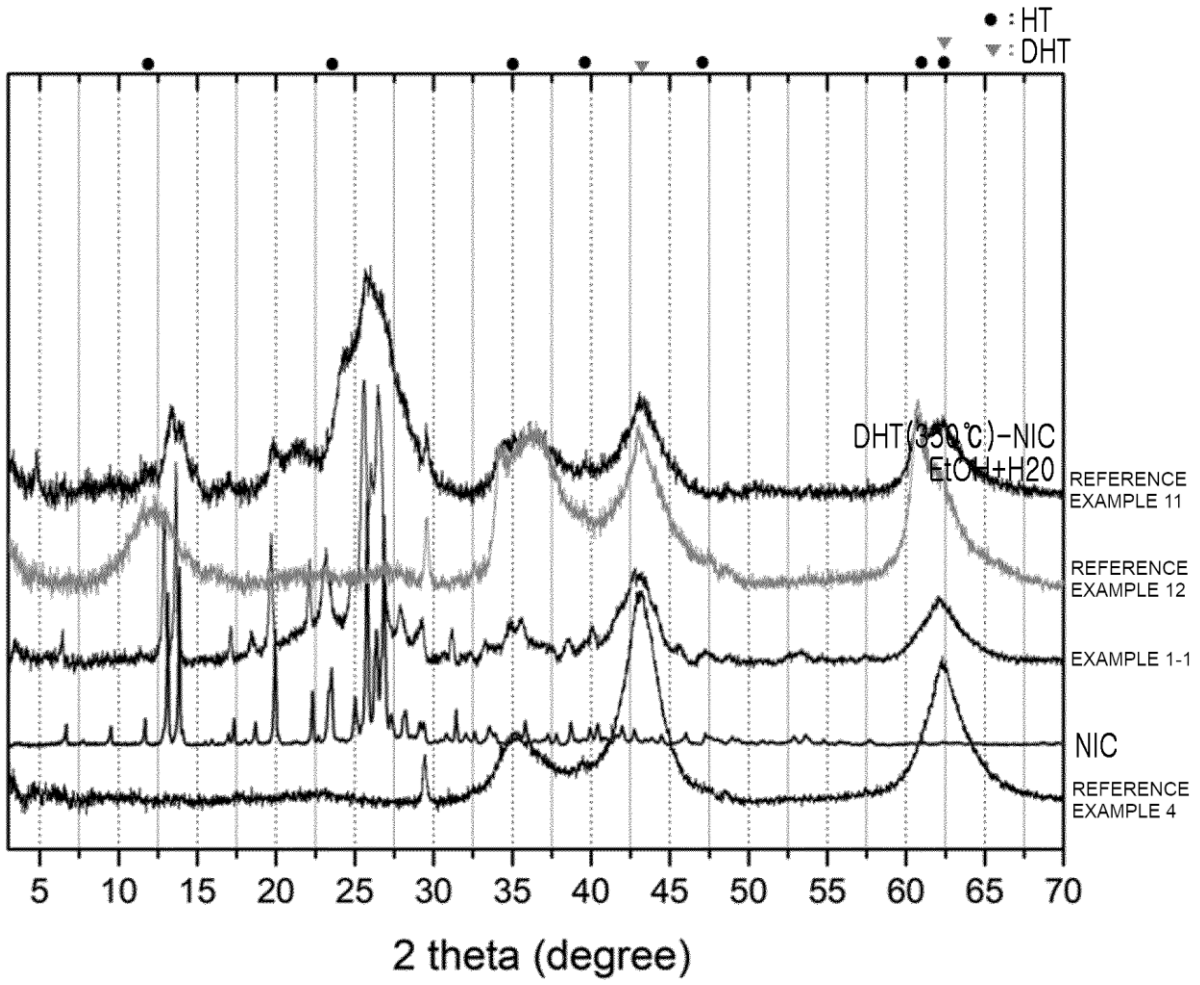

● : HT
▼ : DHT
DHT(350℃)-NIC
EtOH+H20
REFERENCE EXAMPLE 11
REFERENCE EXAMPLE 12
EXAMPLE 1-1
NIC
REFERENCE EXAMPLE 4
5 10 15 20 25 30 35 40 45 50 55 60 65 70
2 theta (degree)

FIG. 12

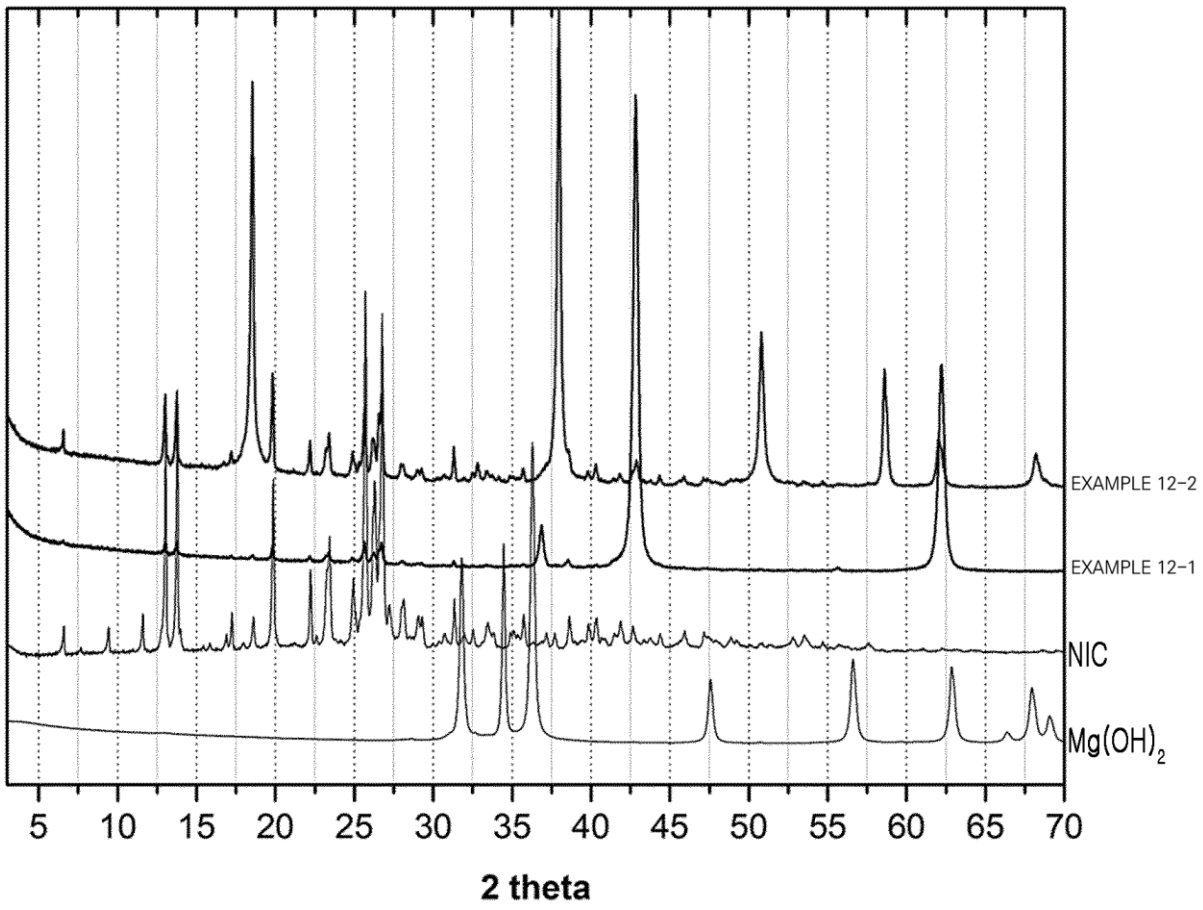

EXAMPLE 12-2
EXAMPLE 12-1
NIC
Mg(OH)2
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta

FIG. 13

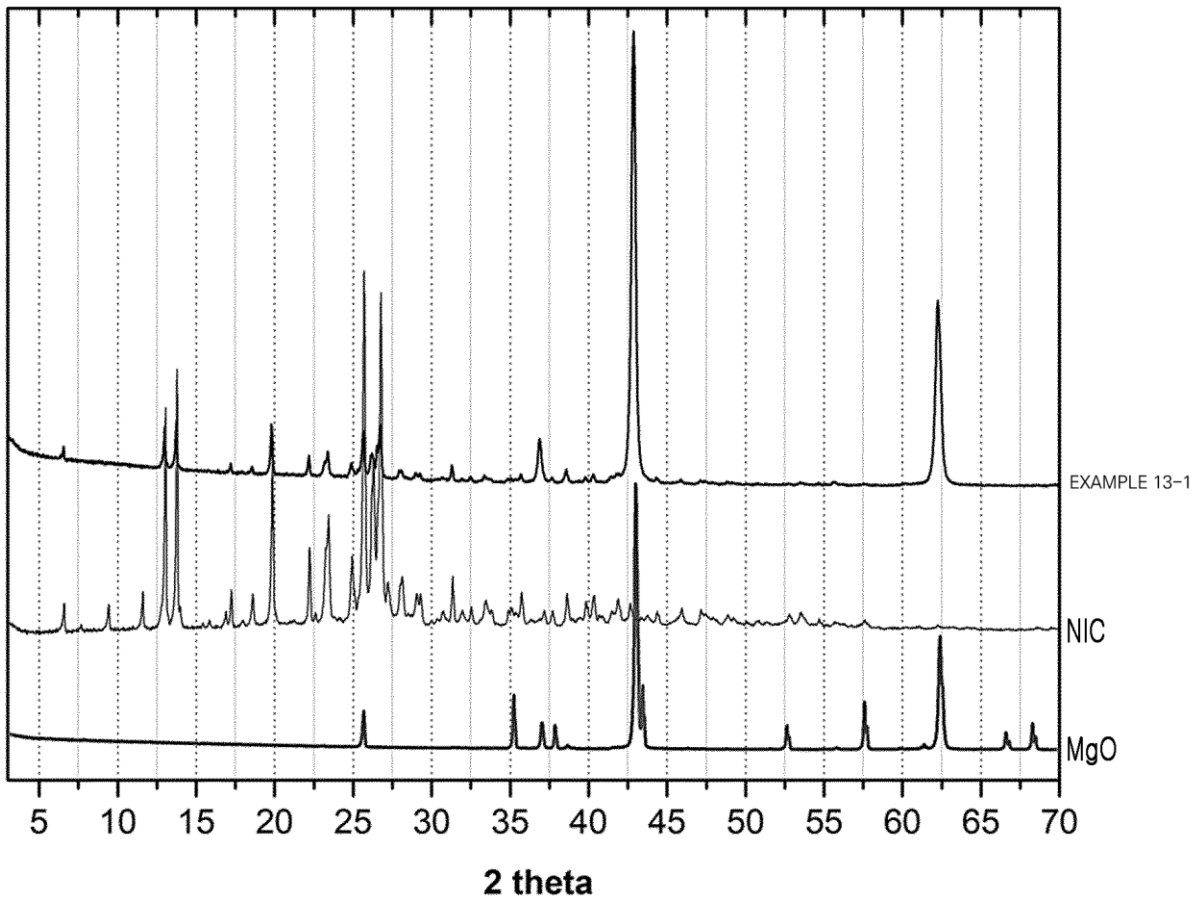



FIG. 14

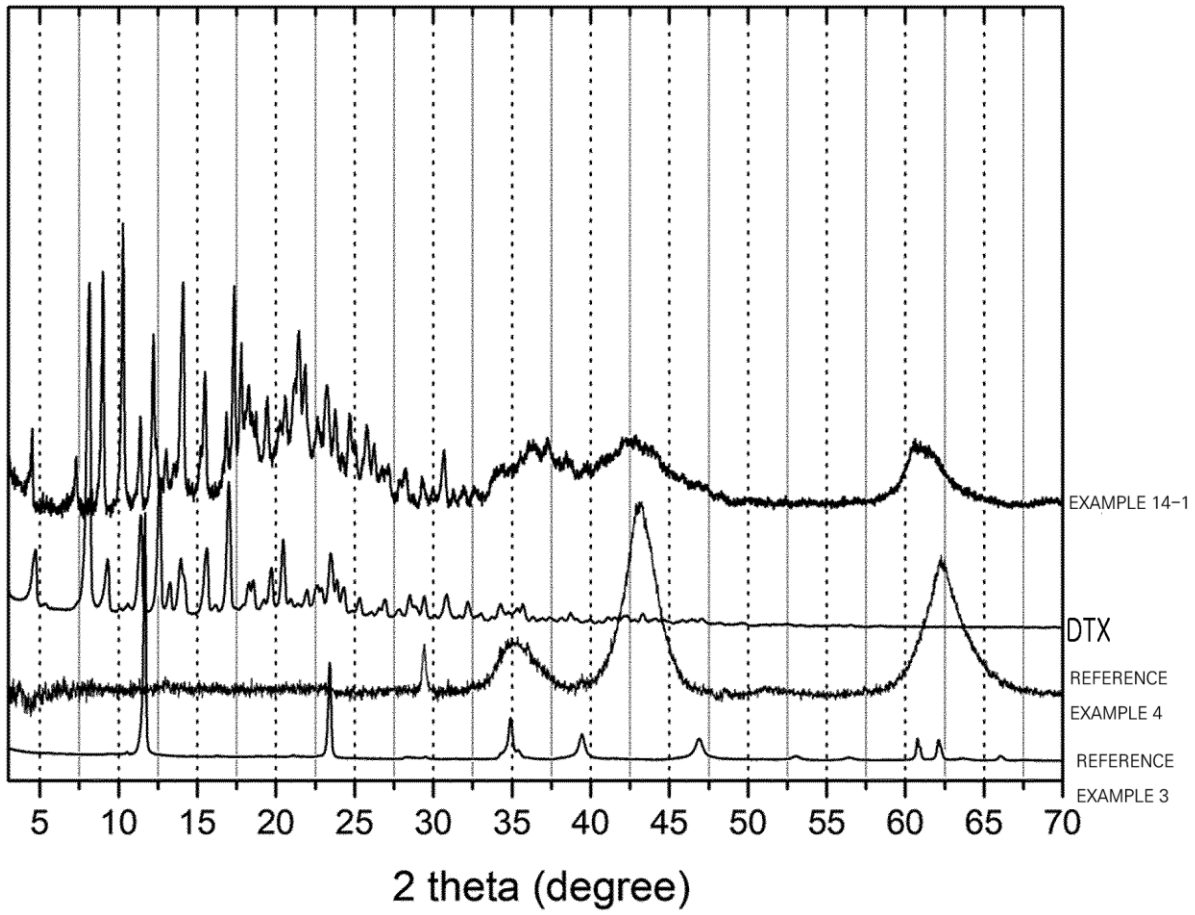

EXAMPLE 14-1
DTX
REFERENCE EXAMPLE 4
REFERENCE EXAMPLE 3
5 10 15 20 25 30 35 40 45 50 55 60 65 70
2 theta (degree)

FIG. 15

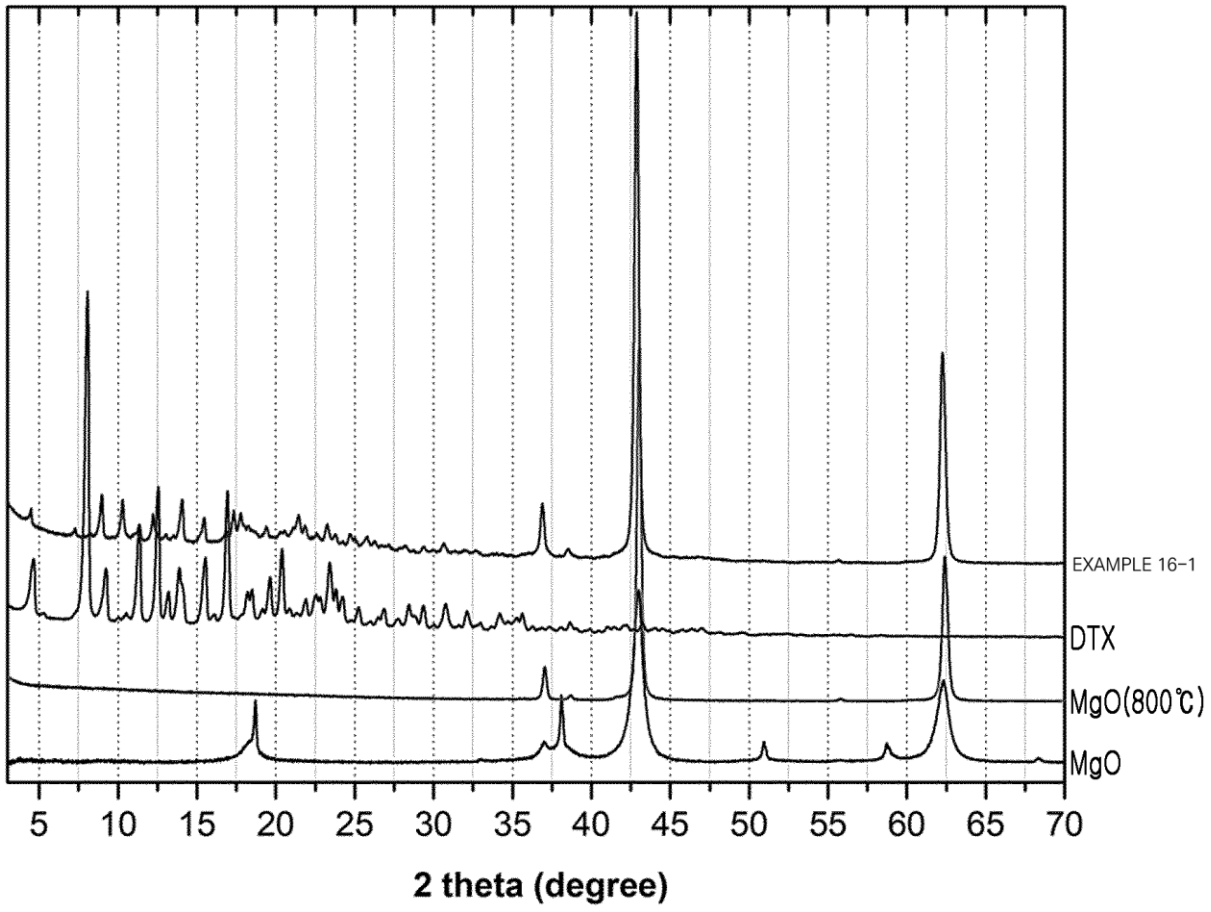

EXAMPLE 16-1
DTX
MgO(800℃)
MgO
5
10
15
20
25
30
35
40
45
50
55
60
65
70
2 theta (degree)

FIG. 16

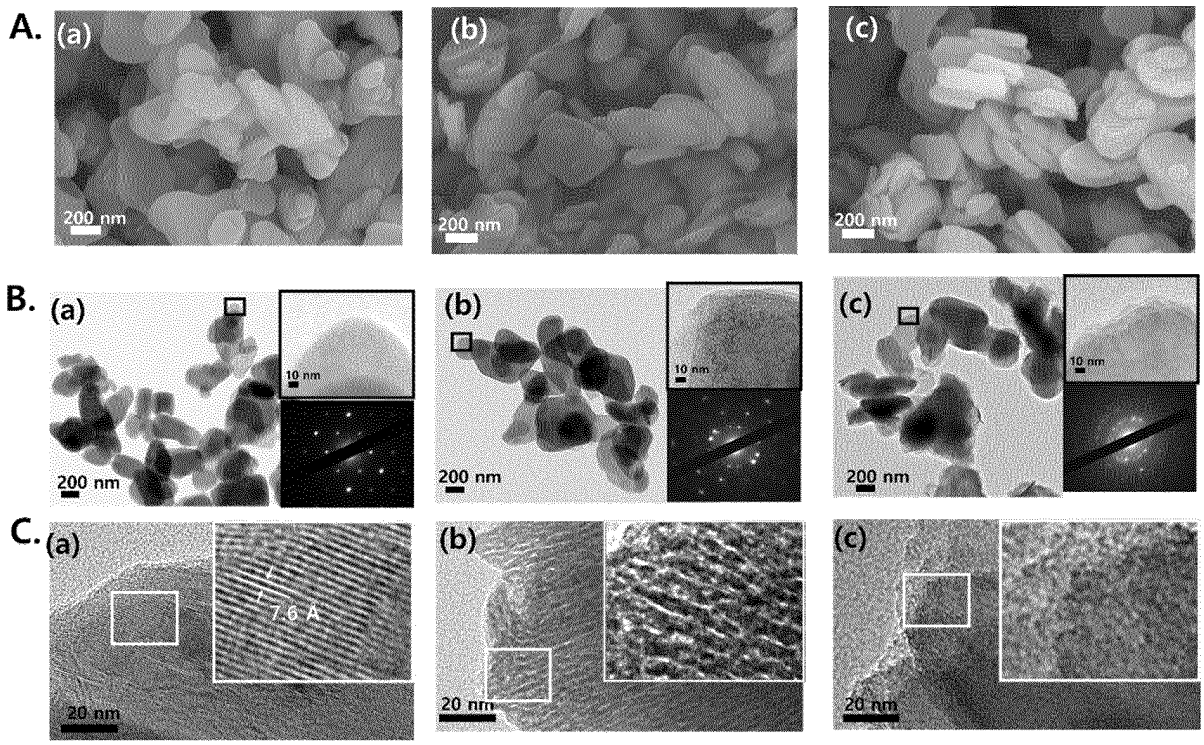

A.
(a)
200 nm
(b)
200 nm
(c)
200 nm
B.
(a)
10 nm
200 nm
(b)
10 nm
200 nm
(c)
10 nm
200 nm
C.
(a)
7.6 Å
20 nm
(b)
20 nm
(c)
20 nm

FIG. 17

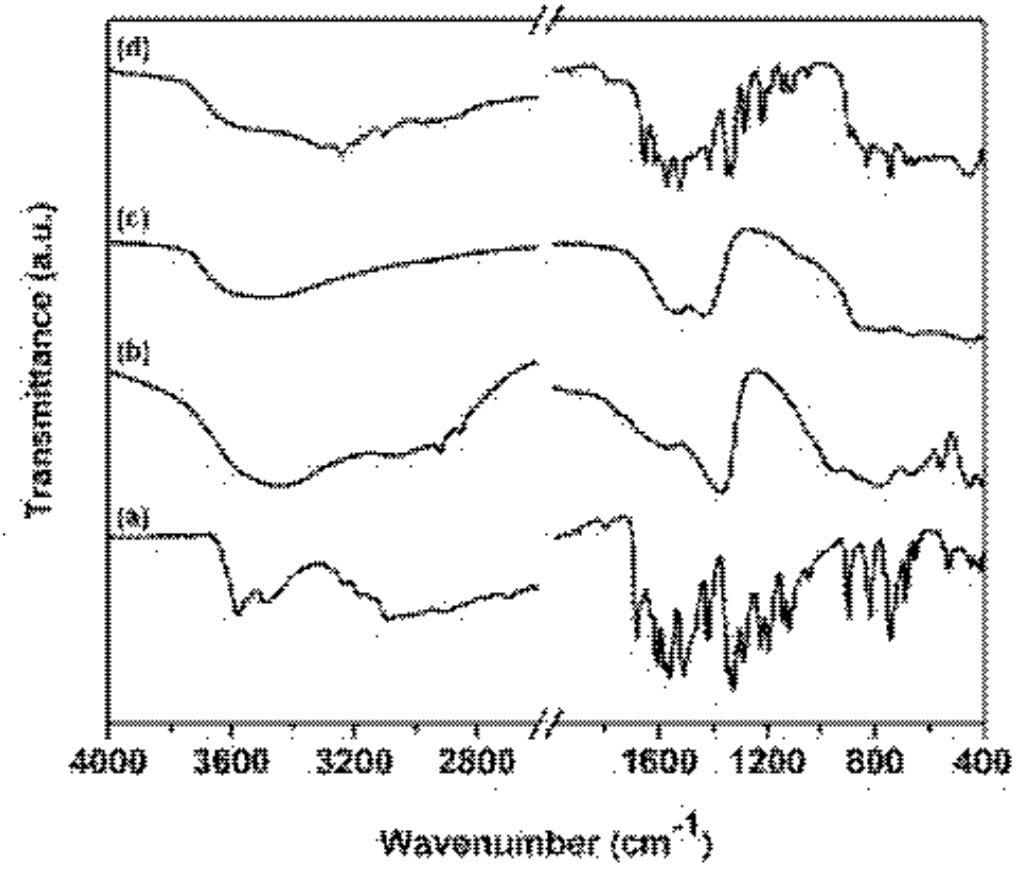

(d)
(c)
(b)
(a)
Transmittance (a.u.)
4000
3600
3200
2800
1600
1200
800
400
Wavenumber (cm-1)

FIG. 18

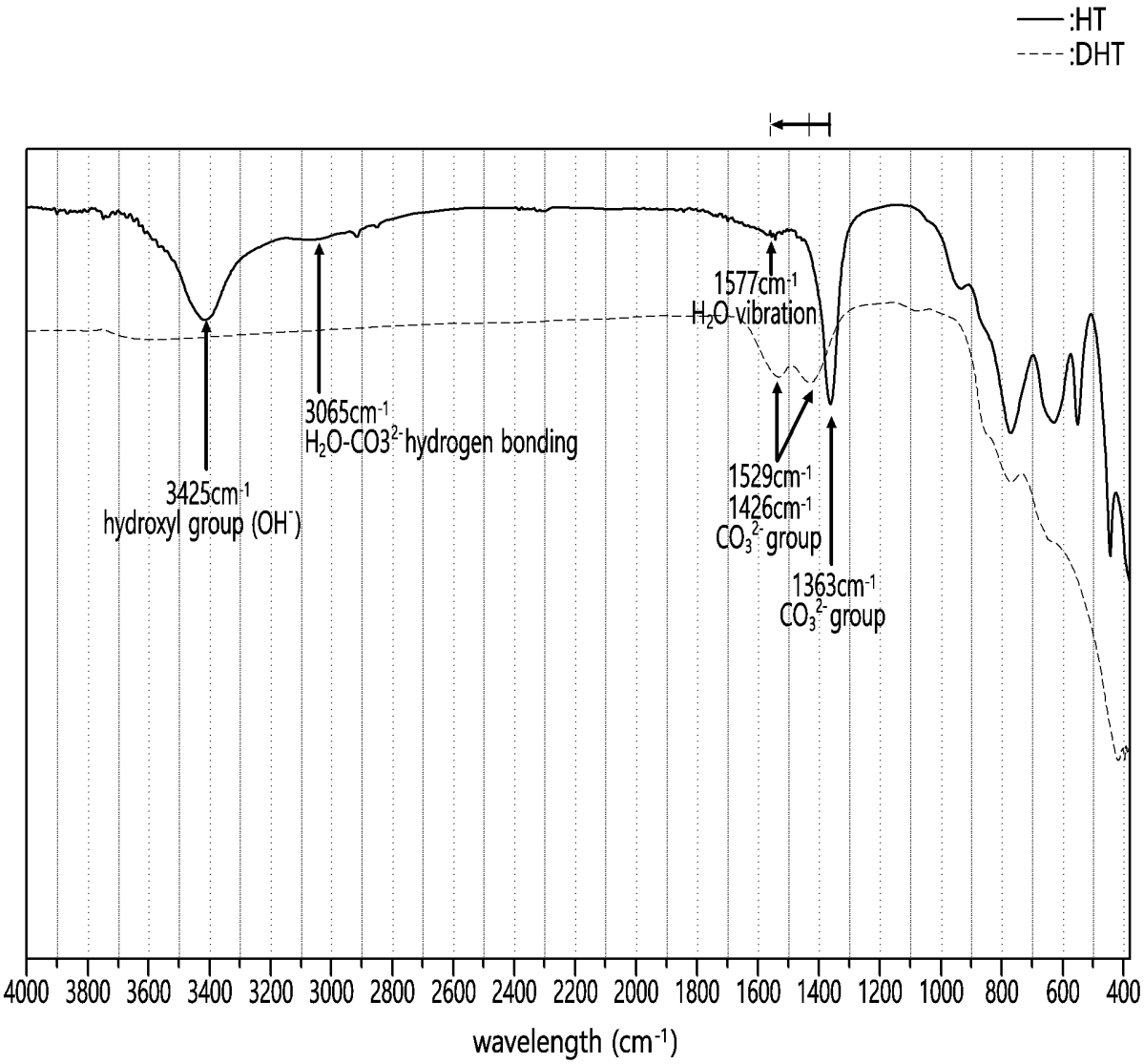

:HT
:DHT
3425cm-1
hydroxyl group (OH-)
3065cm-1
H2O-CO32- hydrogen bonding
1577cm-1
H2O vibration
1529cm-1
1426cm-1
CO32- group
1363cm-1
CO32- group
4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400
wavelength (cm-1)

FIG. 19

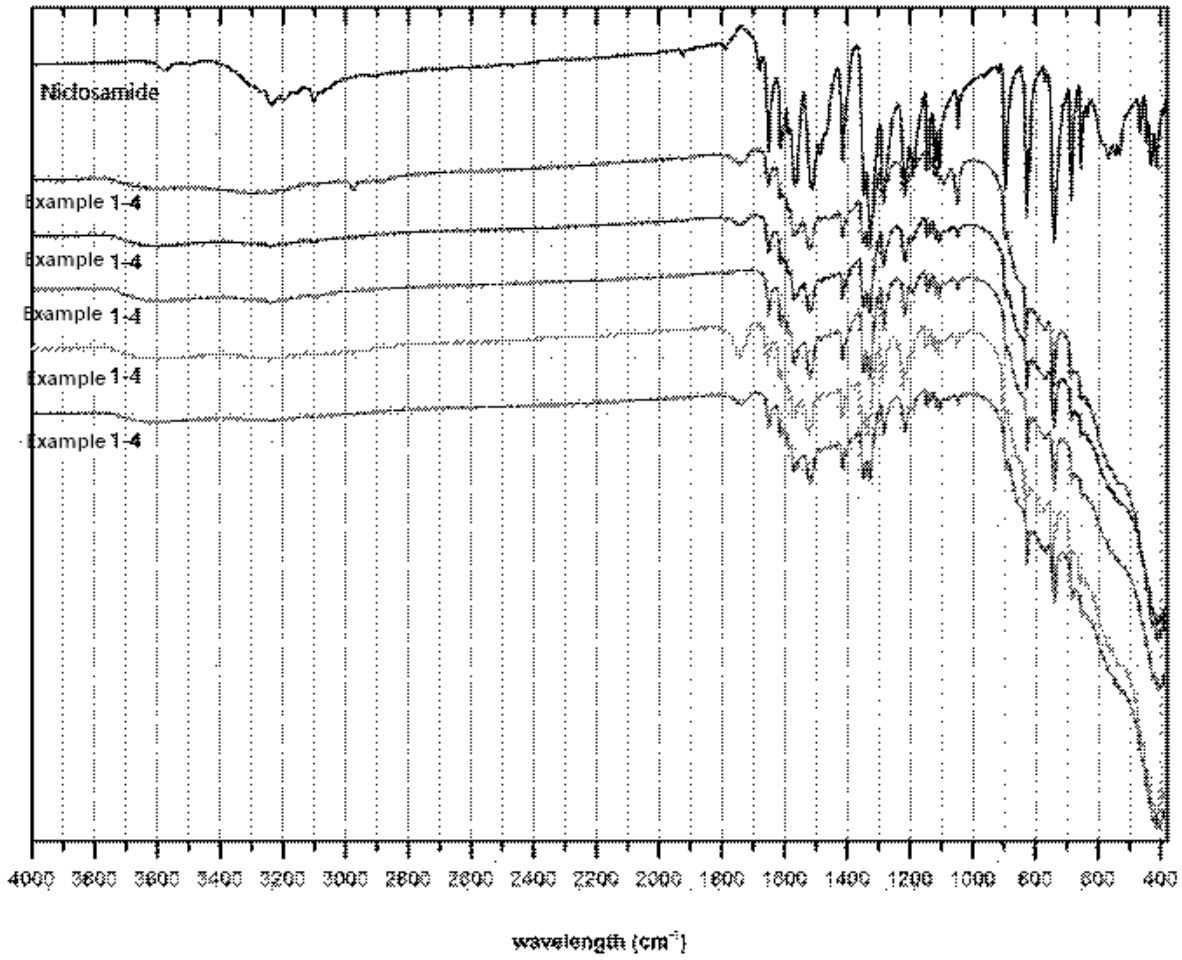

Niclosamide
Example 1-4
Example 1-4
Example 1-4
Example 1-4
Example 1-4
4000 3800 3600 3400 3200 3000 2800 2600 2400 2200 2000 1800 1600 1400 1200 1000 800 600 400
wavelength (cm⁻¹)

FIG. 20

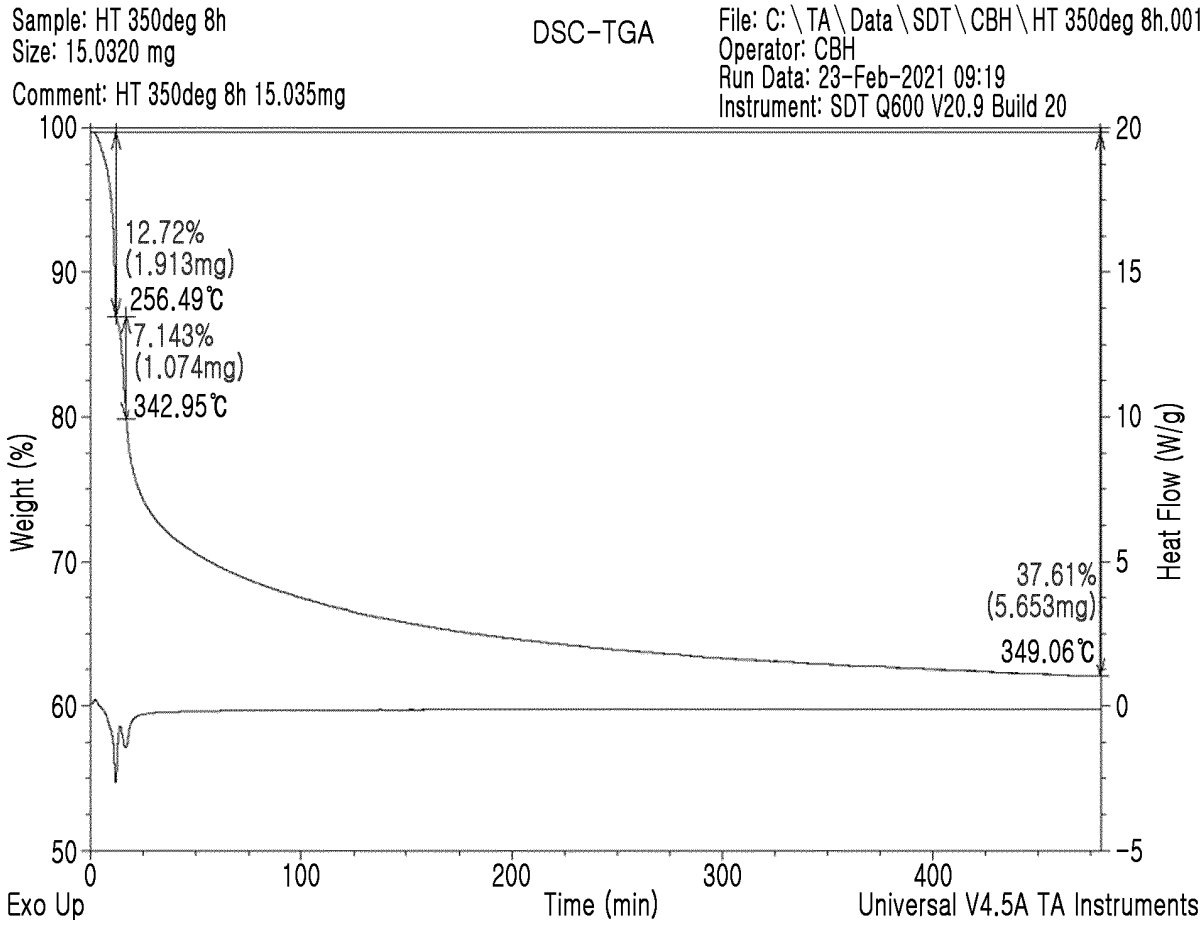

Sample: HT 350deg 8h
Size: 15.0320 mg
Comment: HT 350deg 8h 15.035mg
DSC-TGA
File: C:\TA\Data\SDT\CBH\HT 350deg 8h.001
Operator: CBH
Run Data: 23-Feb-2021 09:19
Instrument: SDT Q600 V20.9 Build 20
12.72%
(1.913mg)
256.49℃
7.143%
(1.074mg)
342.95℃
37.61%
(5.653mg)
349.06℃
Weight (%)
Heat Flow (W/g)
Time (min)
Exo Up
Universal V4.5A TA Instruments

FIG. 21

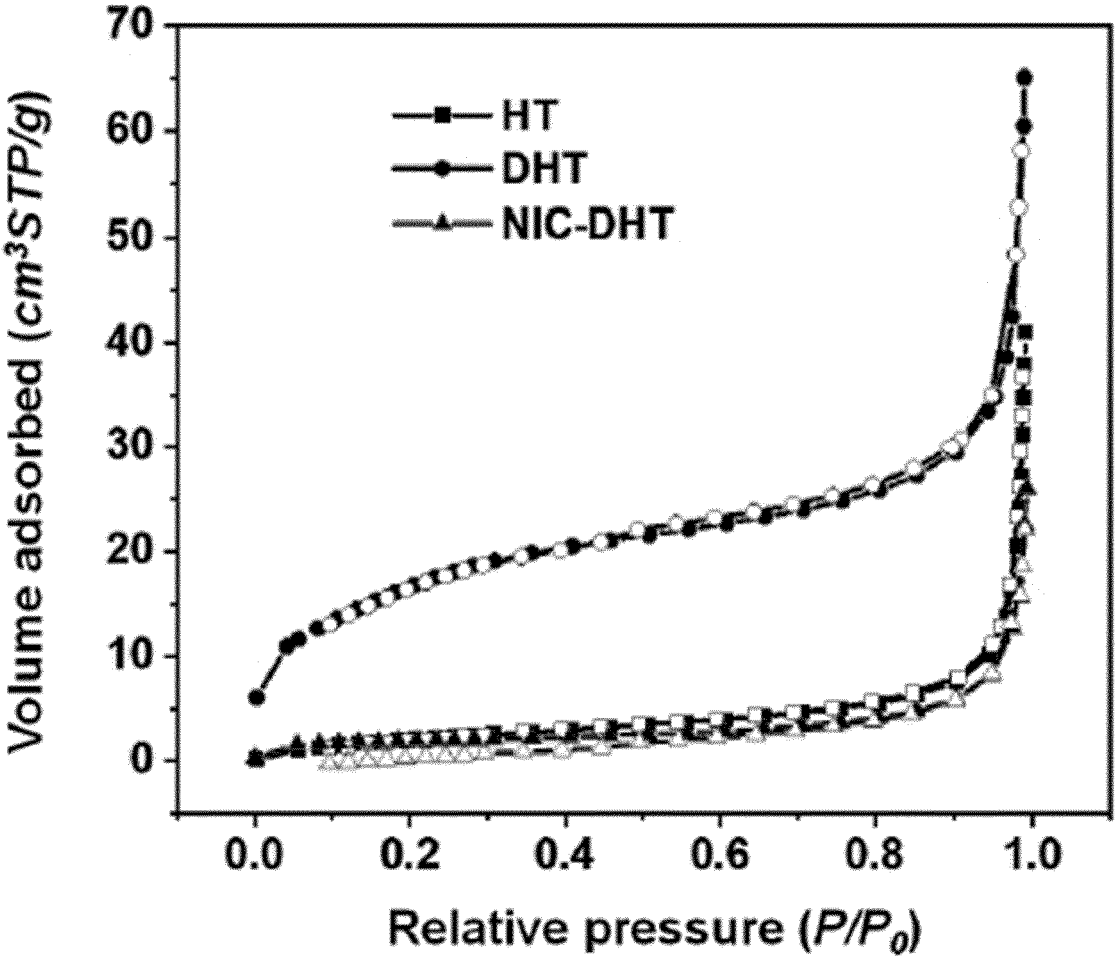

HT
DHT
NIC-DHT
Volume adsorbed ($cm^3STP/g$)
Relative pressure ($P/P_0$)
0
10
20
30
40
50
60
70
0.0
0.2
0.4
0.6
0.8
1.0

FIG. 22

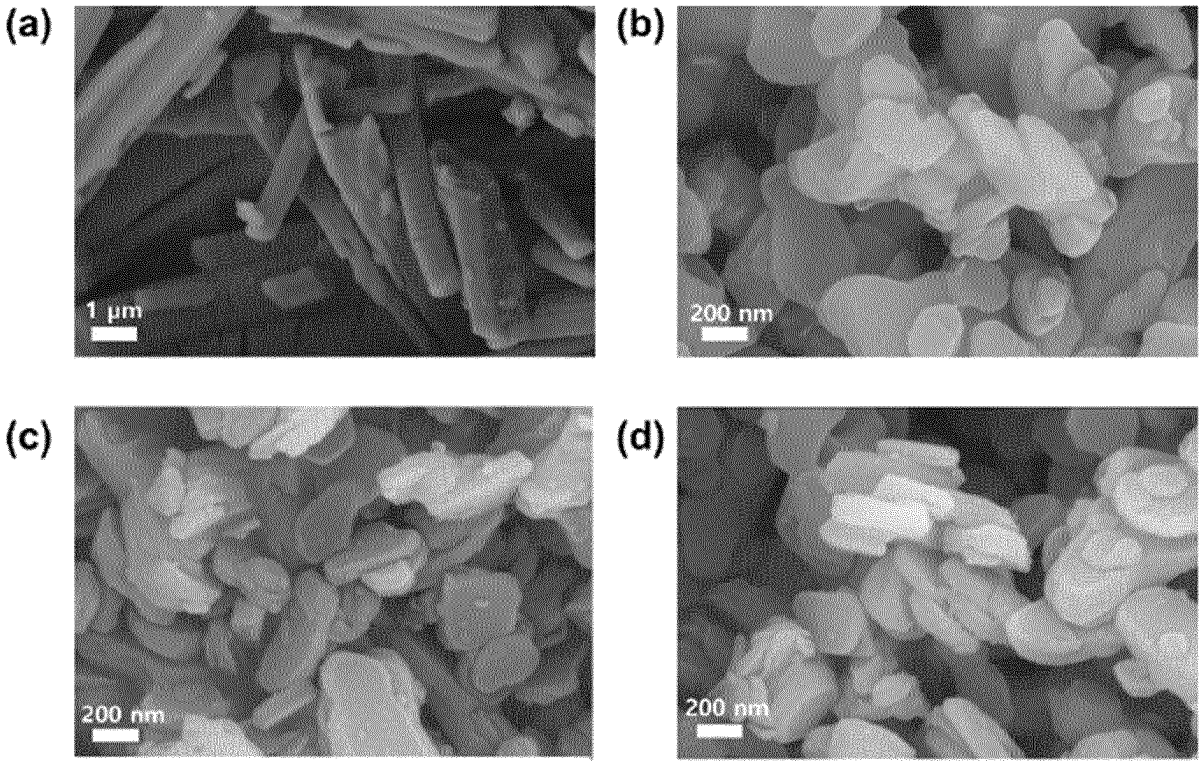



FIG. 23

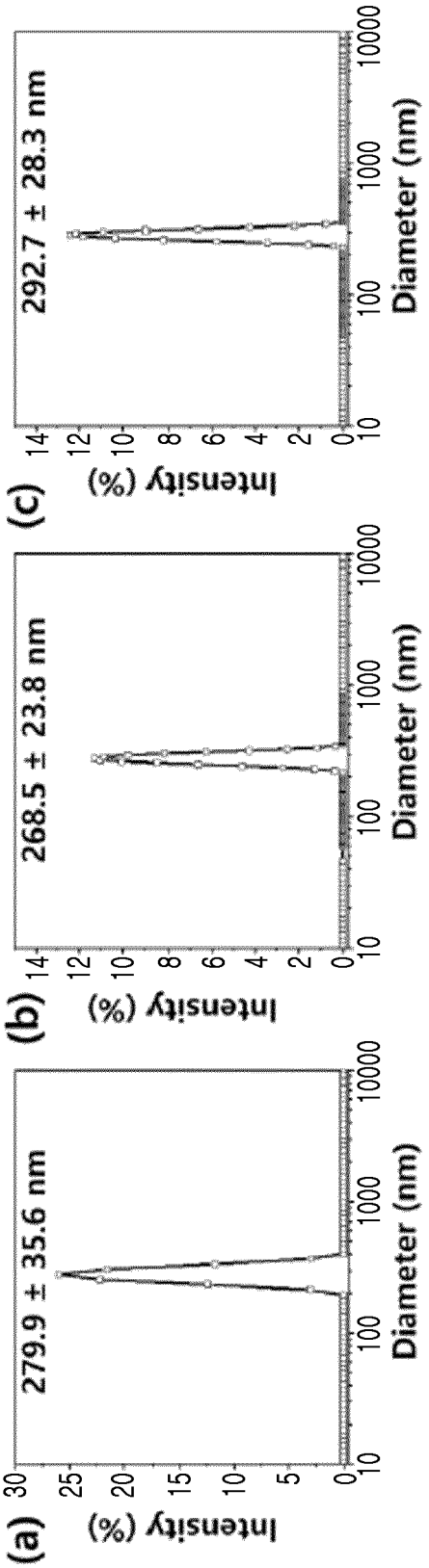

(a)
279.9 ± 35.6 nm
Intensity (%)
Diameter (nm)
(b)
268.5 ± 23.8 nm
Intensity (%)
Diameter (nm)
(c)
292.7 ± 28.3 nm
Intensity (%)
Diameter (nm)

FIG. 24

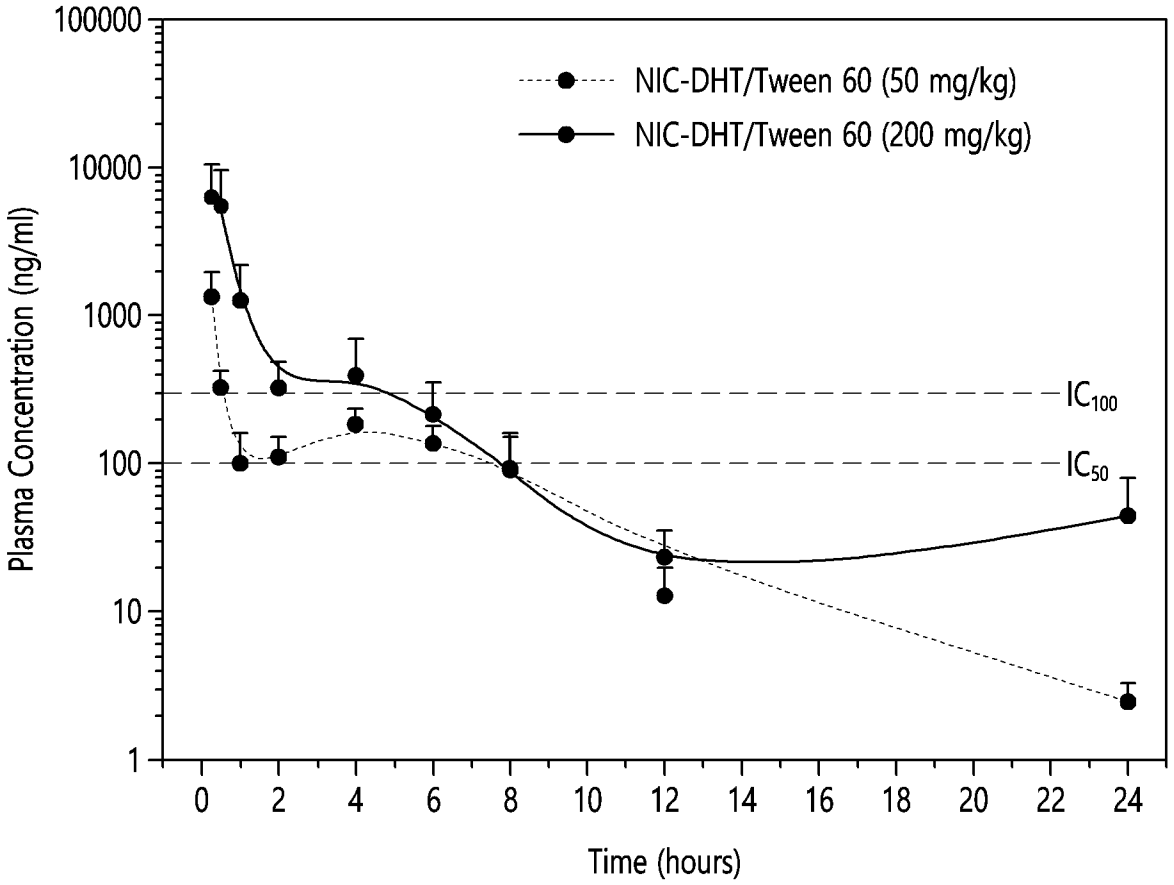
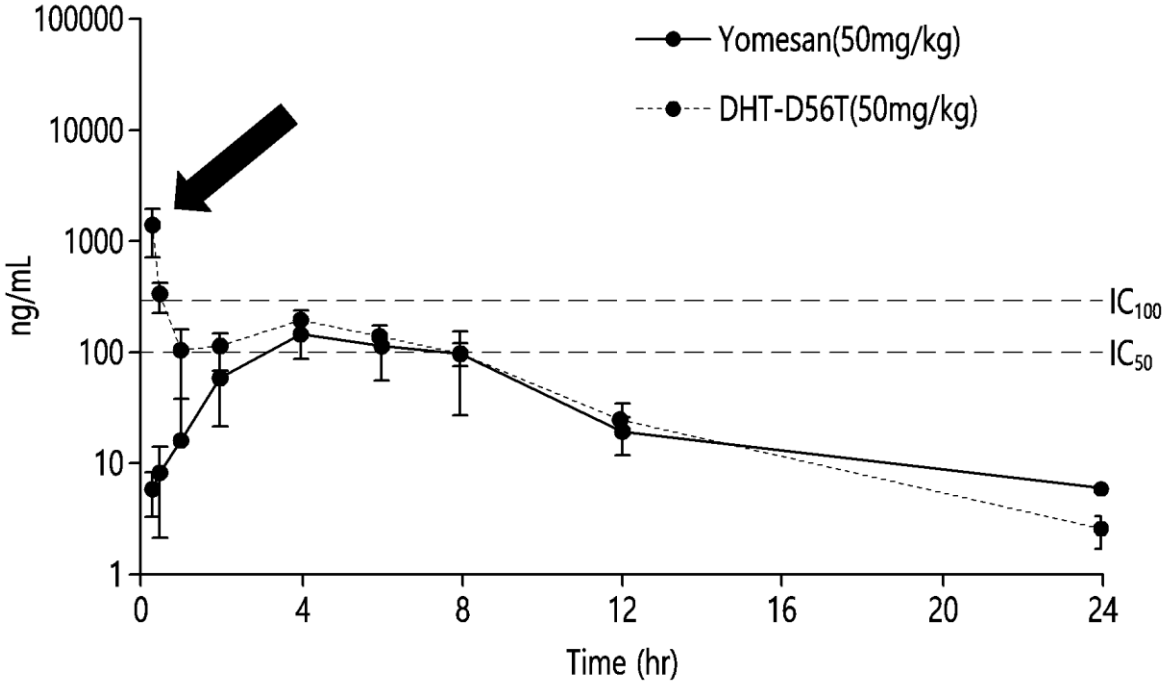
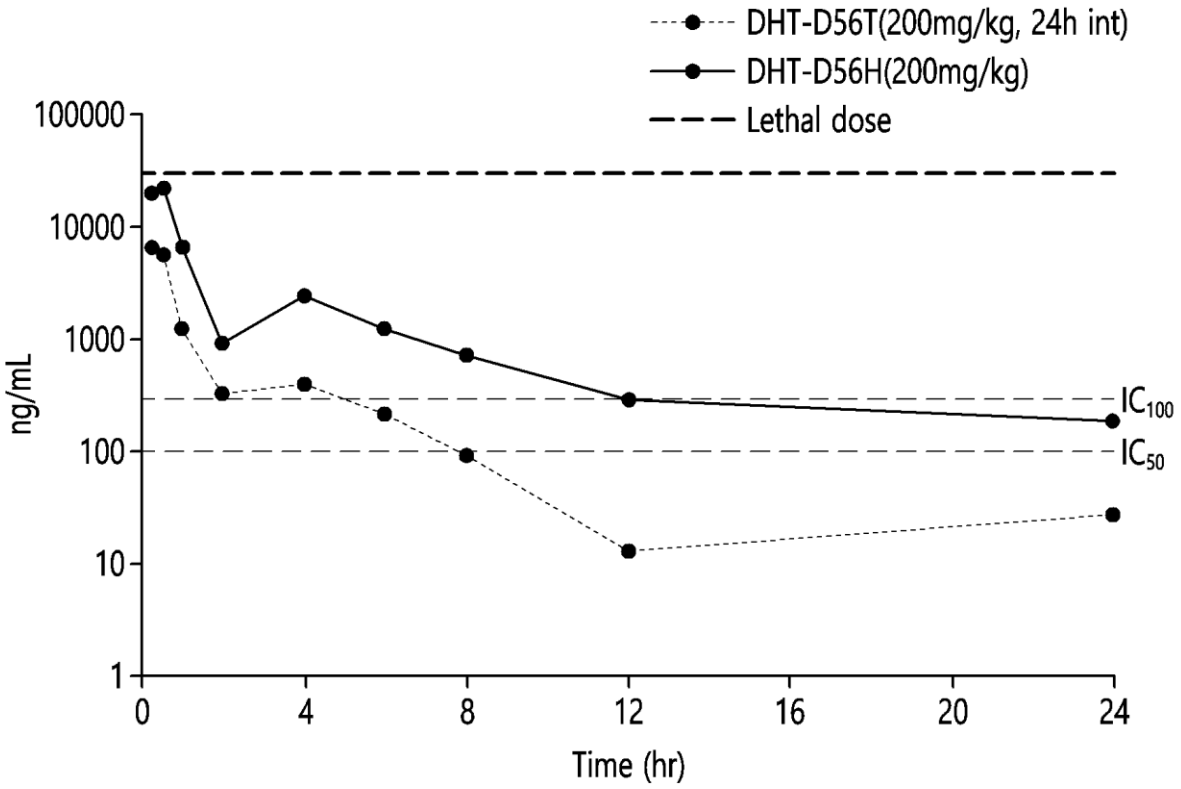

NIC-DHT/Tween 60 (50 mg/kg)
NIC-DHT/Tween 60 (200 mg/kg)
IC100
IC50
Plasma Concentration (ng/ml)
Time (hours)
100000
10000
1000
100
10
1
0
2
4
6
8
10
12
14
16
18
20
22
24

FIG. 25



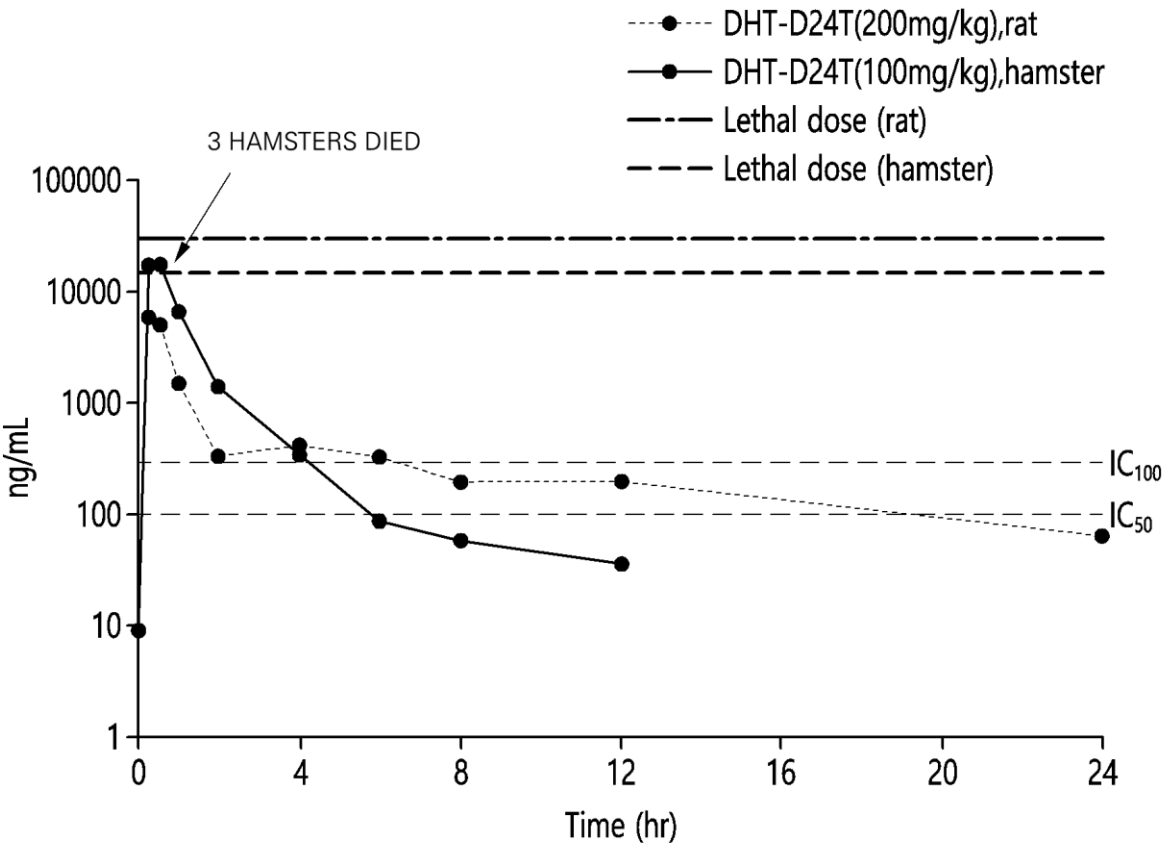

| EFFECT OF DOSAGE FORMING | | | |
|---|---|---|---|
| | Cmax | AUC | note |
| Yomesan | 142.7 | 1096.8 | RESULT OF DOSAGE FORMING<br>Cmax 9.5 times ↑<br>AUC 1.7 times ↑ |
| EXAMPLE 9 (DHT-D56T) | 1350.3 | 1823.8 | |

FIG. 26



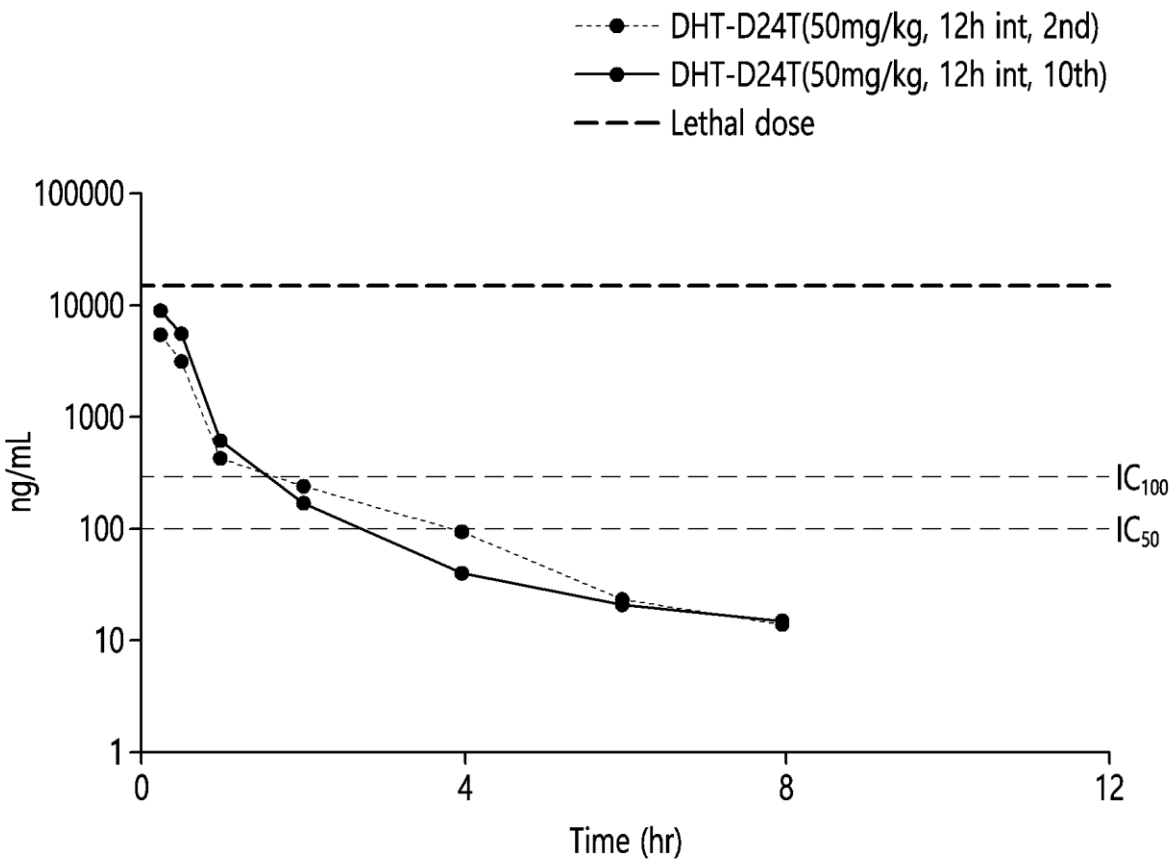

| SURFACTANT EFFECT | | | | |
|---|---|---|---|---|
| | SURFACTANT | Cmax | AUC | note |
| EXAMPLE 9 DHT-D56T | Tween60 | 5481.4 | 6819.3 | Cmax 3.9 times ↑ AND AUC 4.7 times ↑ BY EXCHANGING SURFACTANT WITH HMPC |
| EXAMPLE 6 DHT-D56H | HPMC | 21547.6 | 31863.5 | |

FIG. 27



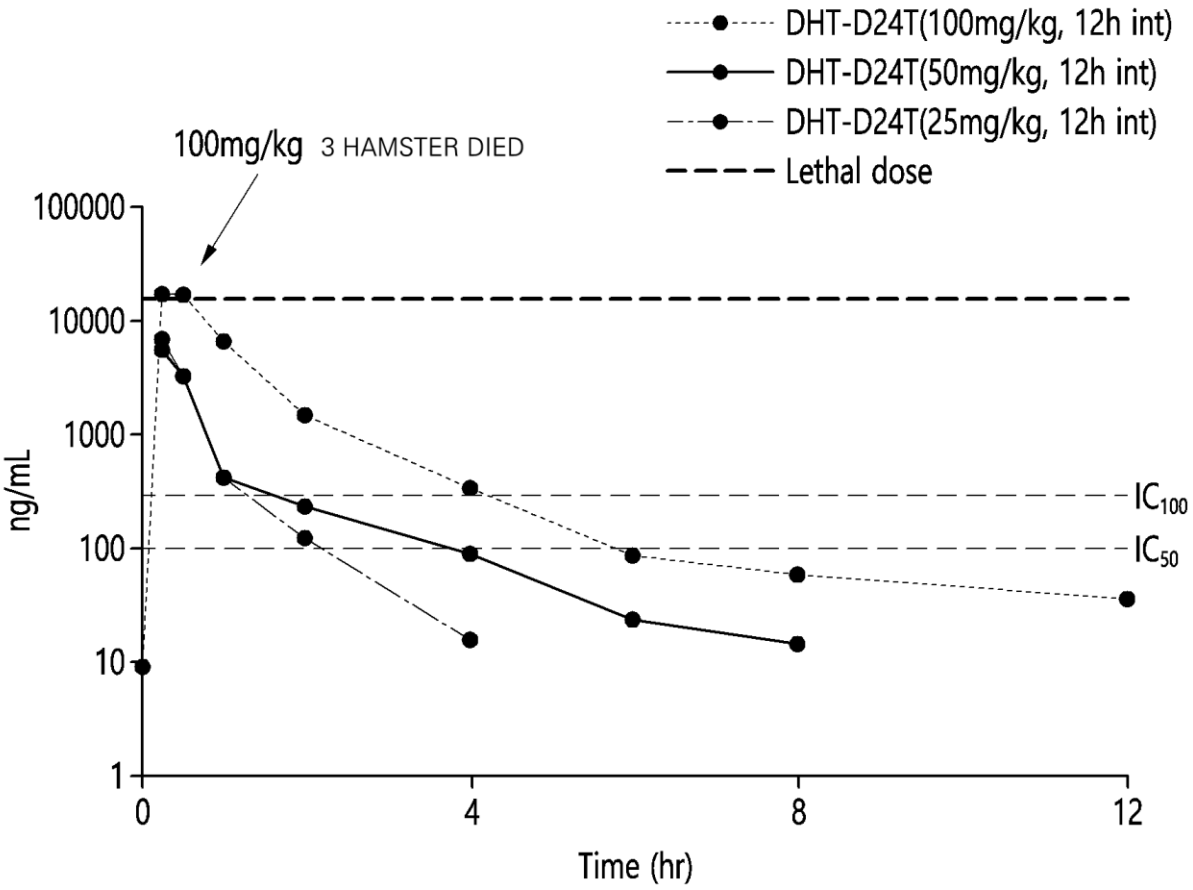

| SPECIES DIFFERENCES | | | | |
|---|---|---|---|---|
| ANIMAL MODEL | DOSE(mg/kg) | Cmax | AUC | Note |
| Rat | 200 | 5883.1 | 8935.0 | AUC ↑ BY ADMINISTERING IT IN DIVIDED DOSES AT FREQUENT INTERVALS |
| Hamster | 100 | 16843.5 | 18425.0 | |

FIG. 28



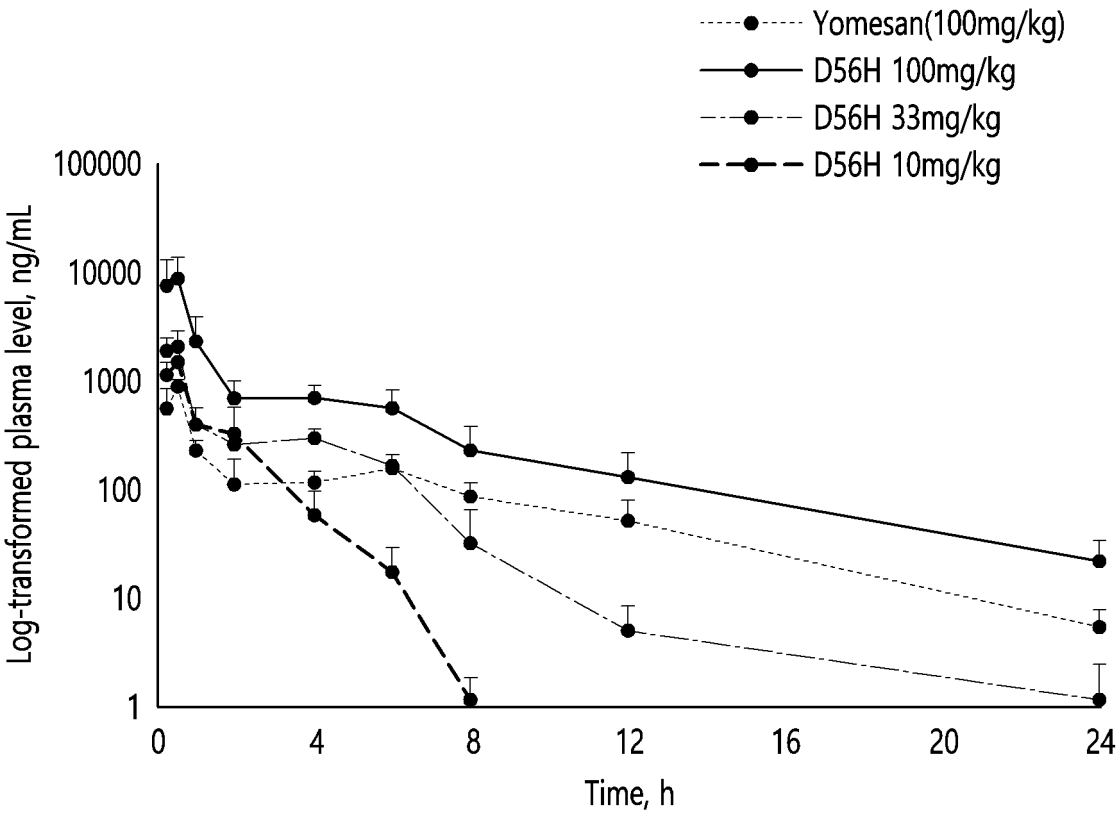

| DOSE DIFFERENCE | | |
|---|---|---|
| NUMBER OF ADMINISTRATINOS | Cmax | AUC |
| 2 | 5372.3 | 3431.3 |
| 10 | 8746.3 | 5102.5 |

FIG. 29



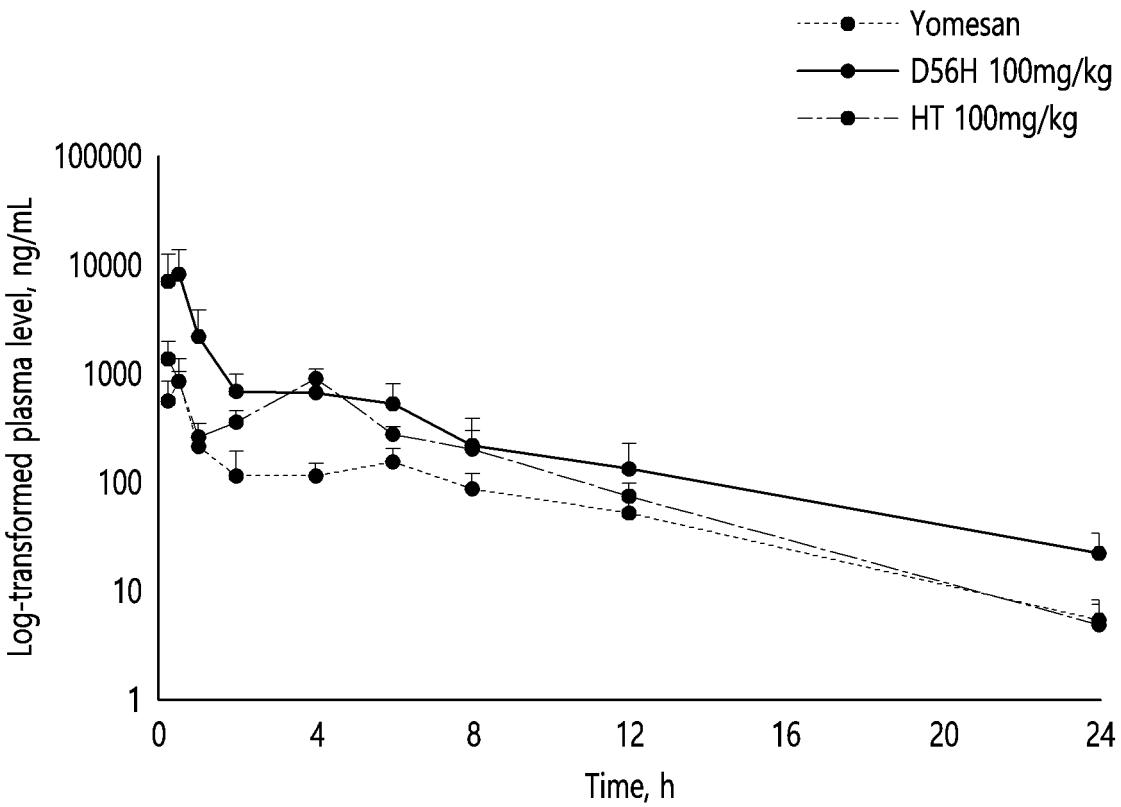

| DOSE DIFFERENCE | | |
|---|---|---|
| DOSE(mg/kg) | Cmax | AUC |
| 25 | 6803.7 | 3381.7 |
| 50 | 5372.3 | 3431.3 |
| 100 | 16843.5 | 18425.0 |

FIG. 30



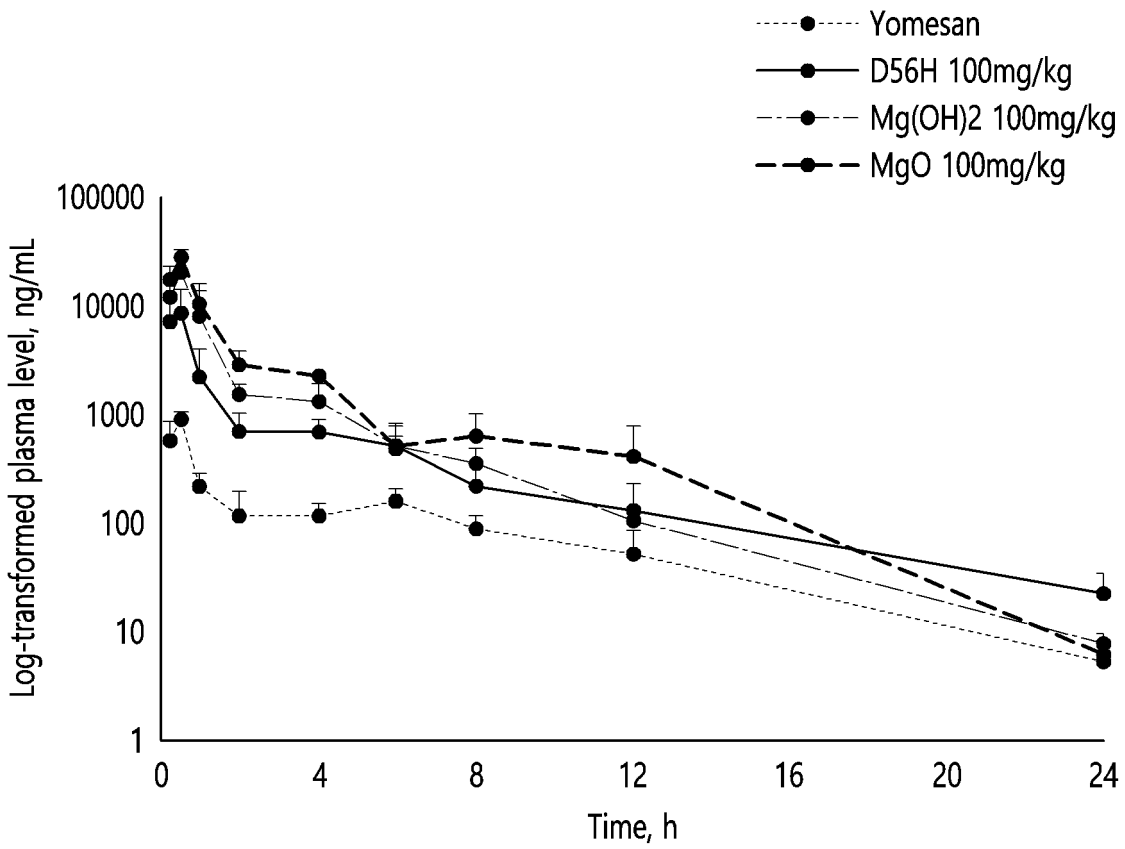

| PK Parameters | Niclosamide, PO | | | |
|---|---|---|---|---|
| | Yomesan | D56H | | |
| | 100 mg/kg | 100 mg/kg | 33 mg/kg | 10 mg/kg |
| AUC(last) | 2010.85 | 11599.26 | 2939.11 | 1702.92 |
| Cmax | 868.84 | 8078.23 | 2308.47 | 1542.97 |
| Tmax | 0.50 | 0.50 | 0.50 | 0.50 |
| $t_{1/2}$ | 4.15 | 4.02 | 3.03 | 0.77 |

FIG. 31



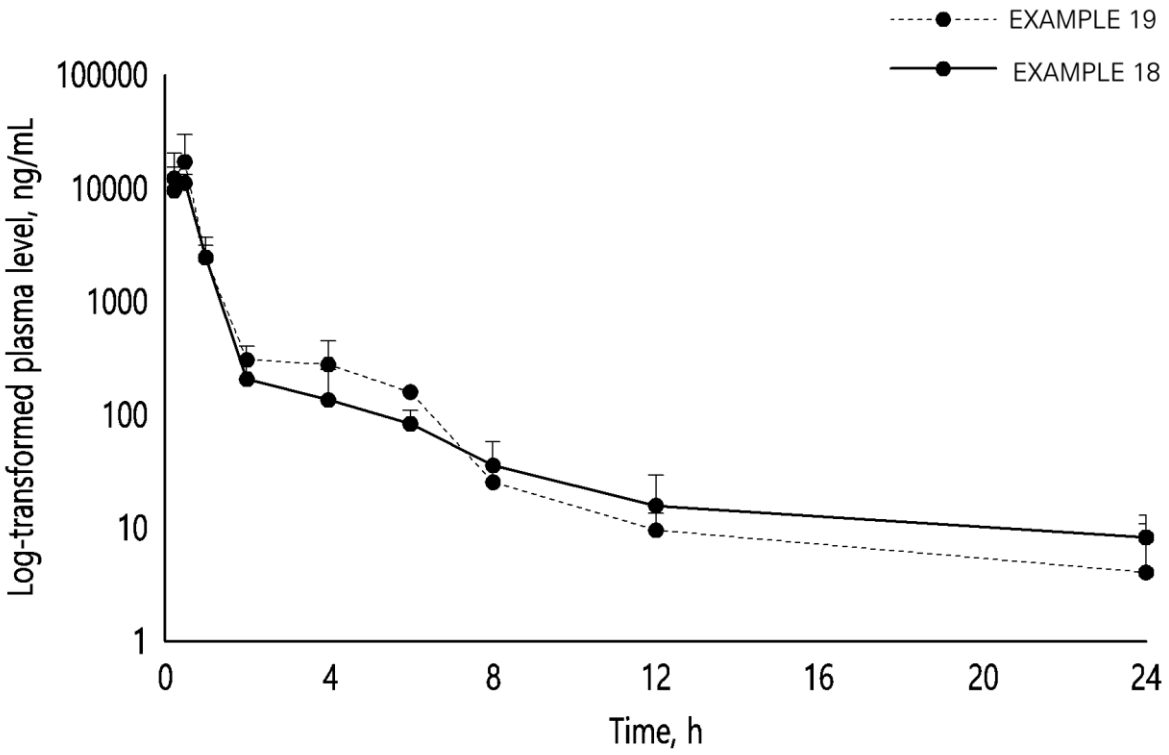

| PK Parameters | Niclosamide, PO | | |
|---|---|---|---|
| | Yomesan | D56H | HT |
| | 100 mg/kg | 100 mg/kg | 100 mg/kg |
| AUC(last) | 2010.85 | 11599.26 | 4919.93 |
| Cmax | 868.84 | 8078.23 | 1487.80 |
| Tmax | 0.50 | 0.50 | 0.25 |
| $t_{1/2}$ | 4.15 | 4.02 | 3.06 |

FIG. 32




| PK Parameters | Niclosamide, PO | | | |
|---|---|---|---|---|
| | Yomesan | D56H | Mg(OH)2 | MgO |
| | 100 mg/kg | 100 mg/kg | 100 mg/kg | 100 mg/kg |
| AUC(last) | 2010.85 | 11599.26 | 22437.26 | 33797.23 |
| Cmax | 868.84 | 8078.23 | 17828.61 | 21438.78 |
| Tmax | 0.50 | 0.50 | 0.50 | 0.50 |
| $t_{1/2}$ | 4.15 | 4.02 | 2.67 | 2.37 |

FIG. 33




| PK Parameters | Niclosamide PO 100 mg/kg | |
|---|---|---|
| | EXAMPLE 19 | EXAMPLE 18 |
| AUC(last) | 17206.82 | 18311.94 |
| Cmax | 14805.71 | 17694.34 |
| Tmax | 0.50 | 0.50 |
| $t_{1/2}$ | 17.36 | 8.20 |

FIG. 34

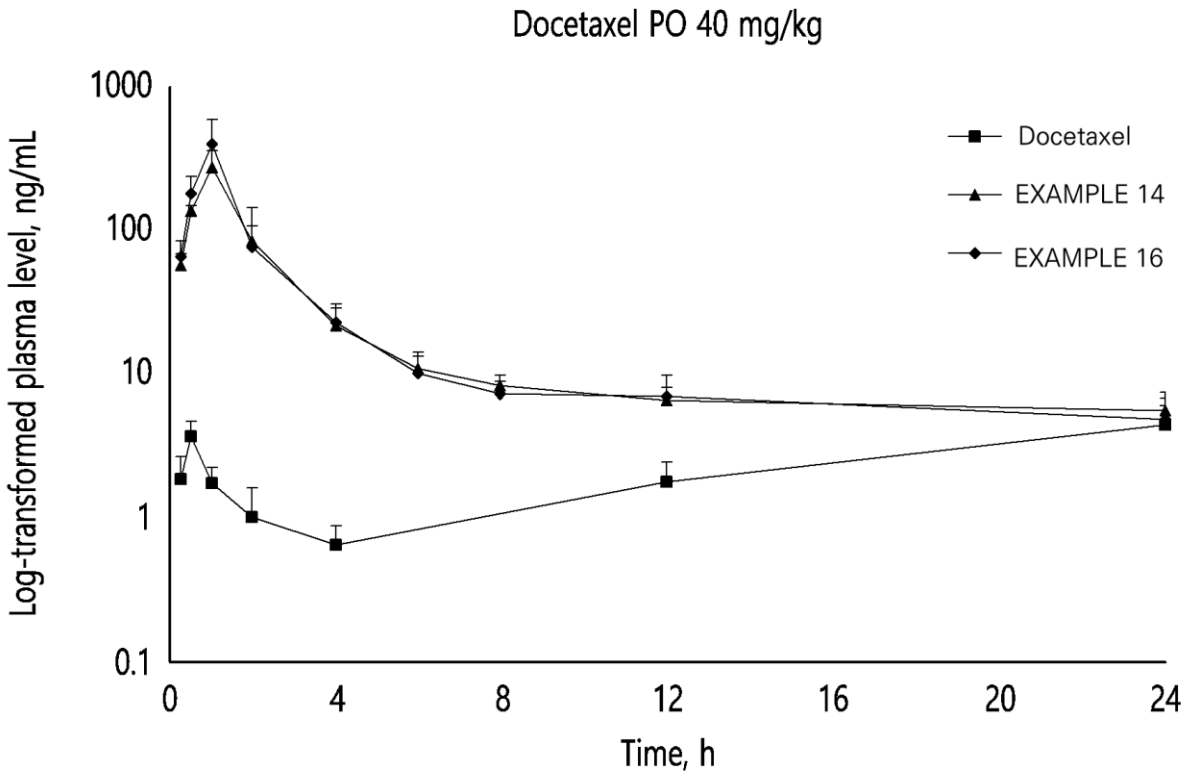

Docetaxel PO 40 mg/kg
Log-transformed plasma level, ng/mL
1000
100
10
1
0.1
0
4
8
12
16
20
24
Time, h
Docetaxel
EXAMPLE 14
EXAMPLE 16

FIG. 35

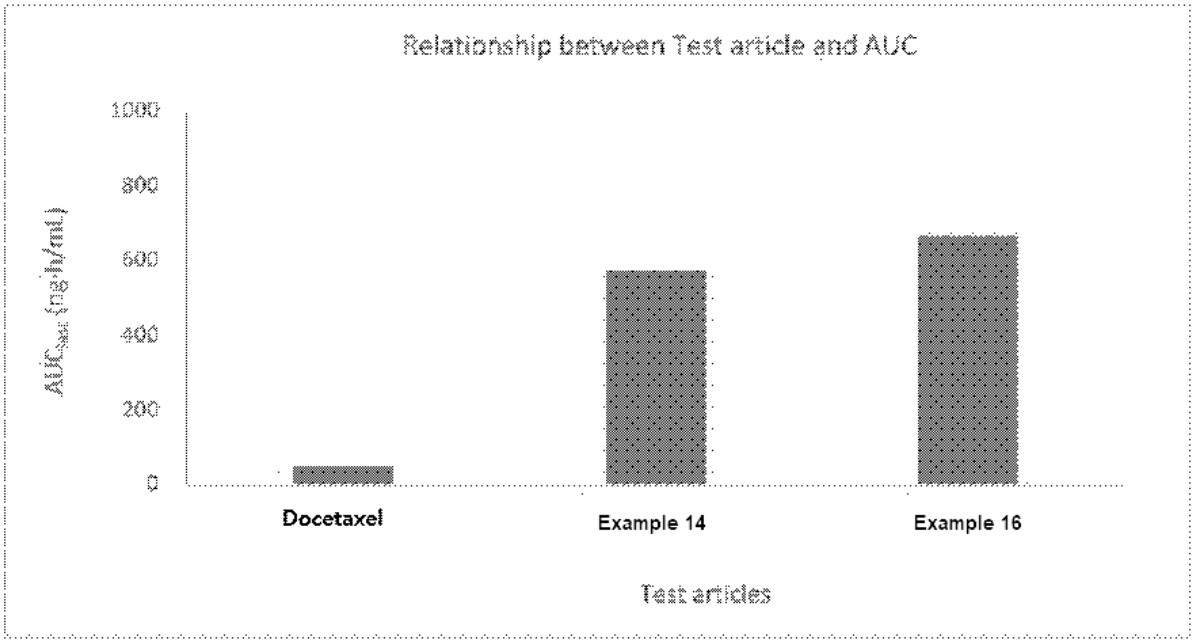

Relationship between Test article and AUC
1000
800
600
400
200
0
AUC$_{last}$ (ng·h/mL)
Docetaxel
Example 14
Example 16
Test articles

FIG. 36

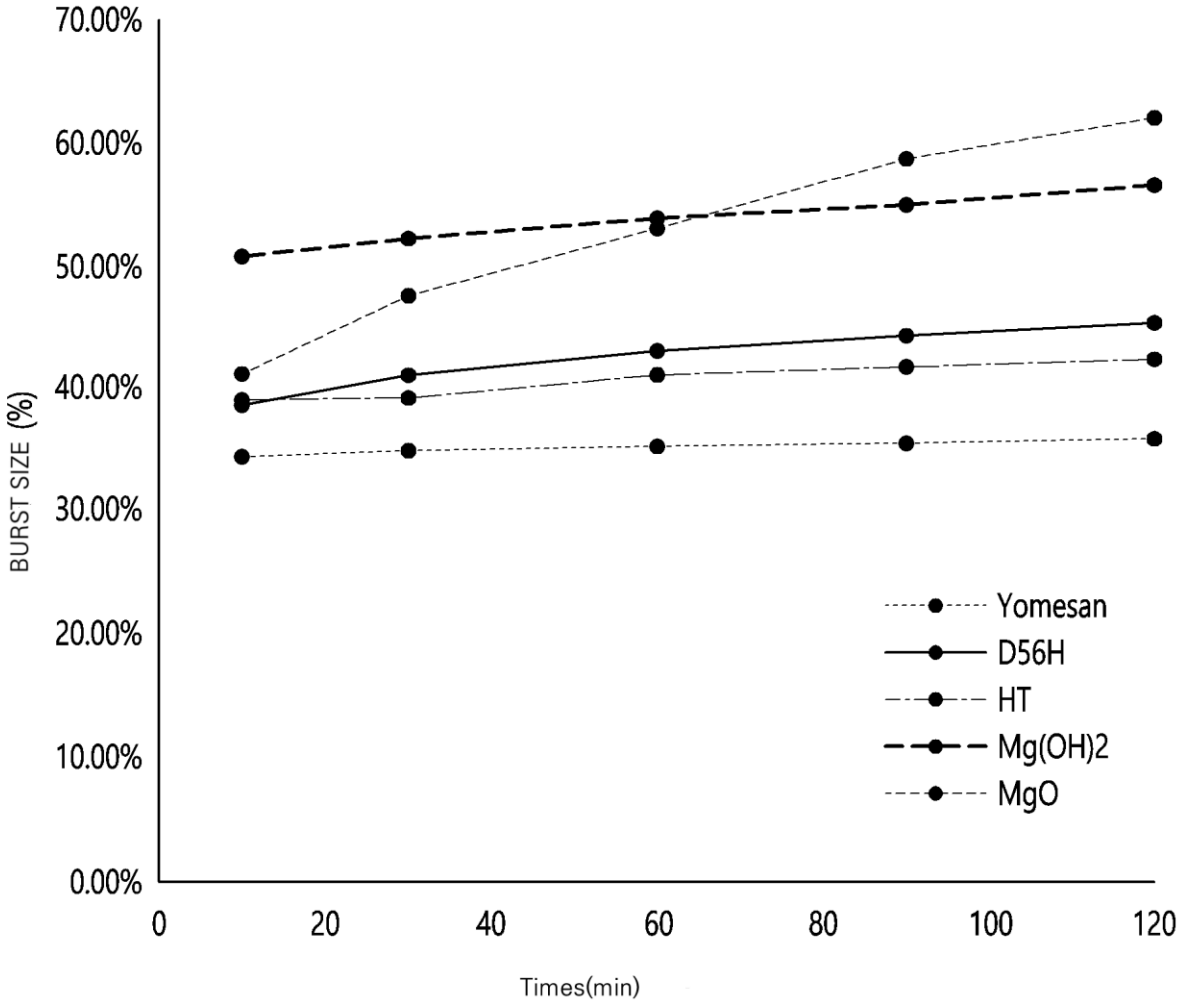

70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
BURST SIZE (%)
0
20
40
60
80
100
120
Times(min)
Yomesan
D56H
HT
Mg(OH)2
MgO

FIG. 37

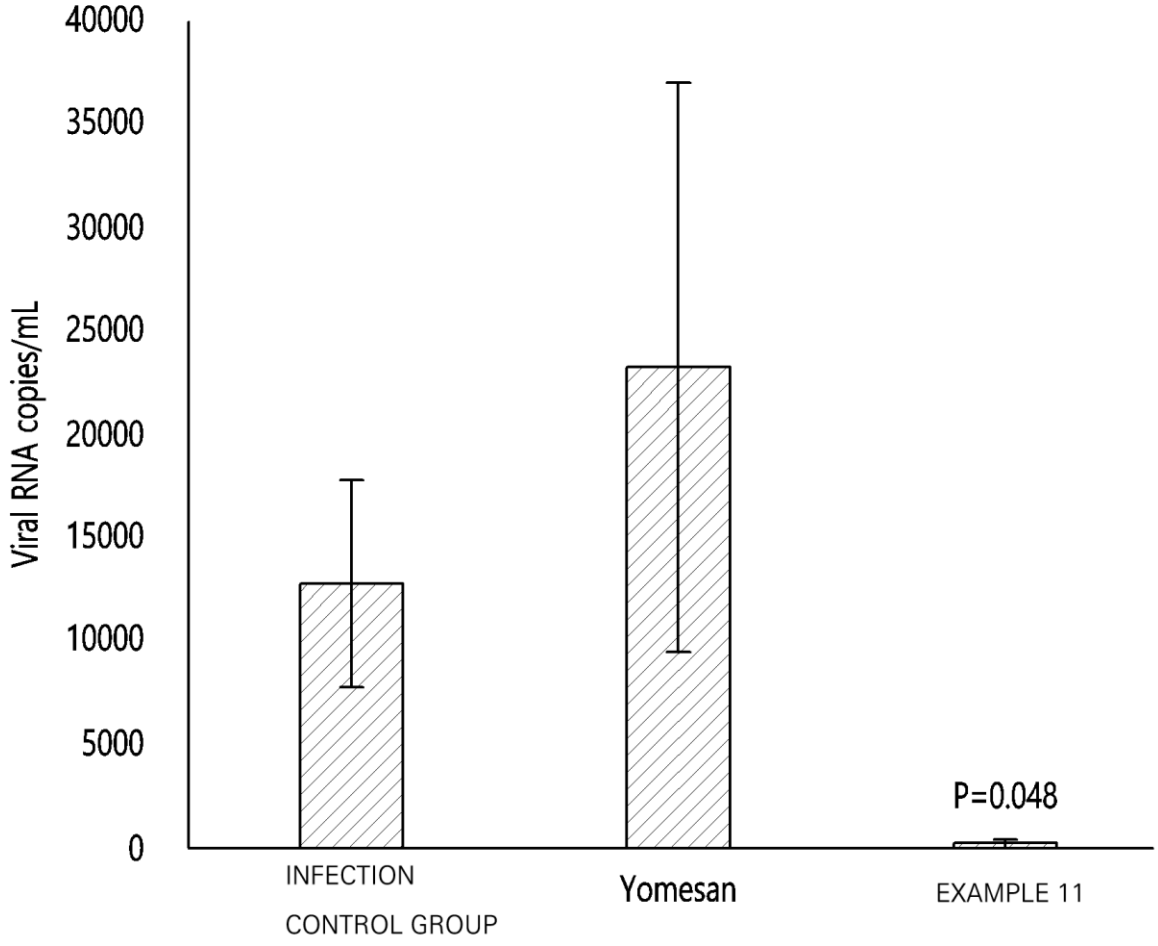

40000
35000
30000
25000
20000
15000
10000
5000
0
Viral RNA copies/mL
P=0.048
INFECTION CONTROL GROUP
Yomesan
EXAMPLE 11

FIG. 38

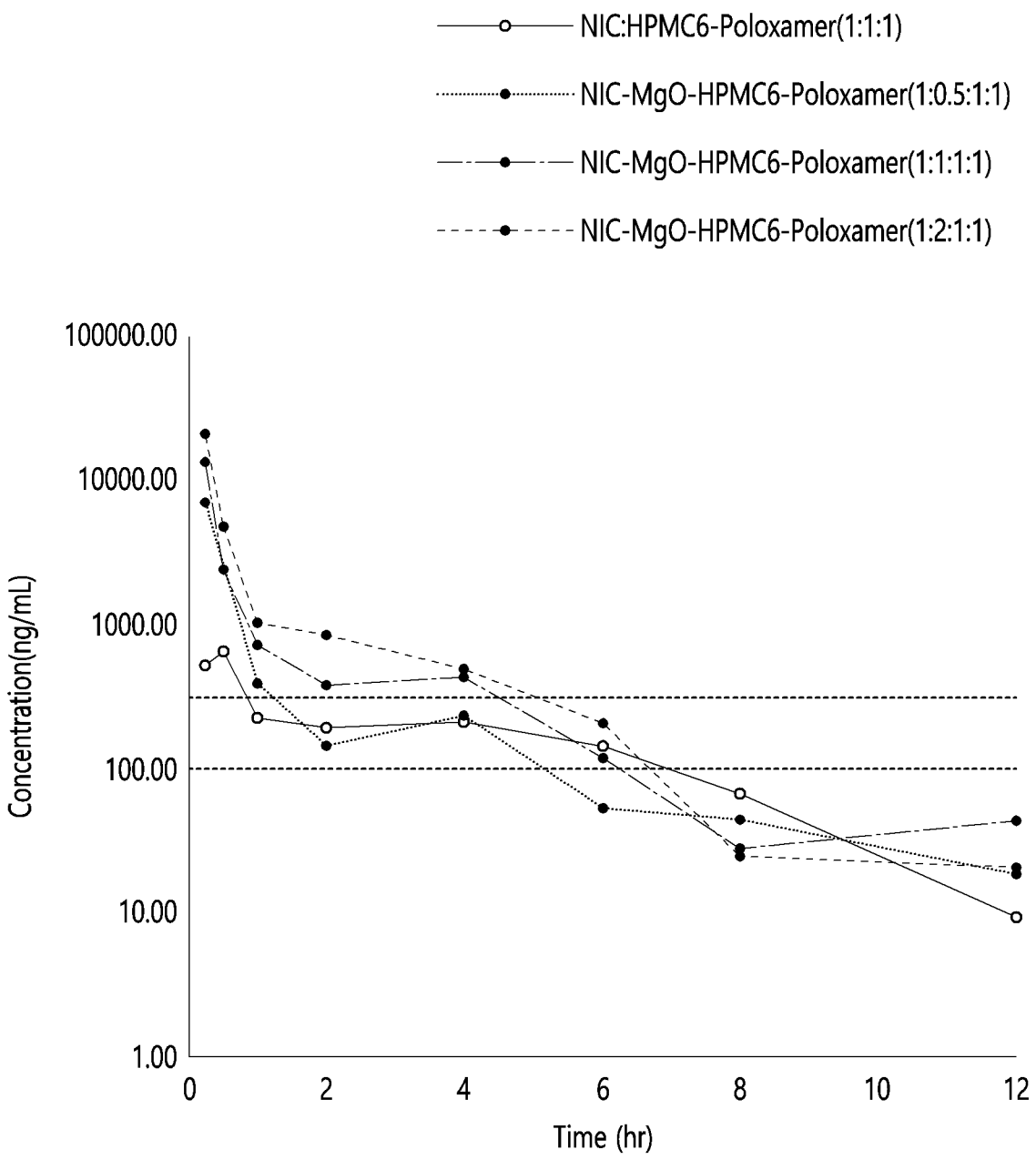

NIC:HPMC6-Poloxamer(1:1:1)
NIC-MgO-HPMC6-Poloxamer(1:0.5:1:1)
NIC-MgO-HPMC6-Poloxamer(1:1:1:1)
NIC-MgO-HPMC6-Poloxamer(1:2:1:1)
100000.00
10000.00
1000.00
100.00
10.00
1.00
Concentration(ng/mL)
0
2
4
6
8
10
12
Time (hr)

FIG. 39

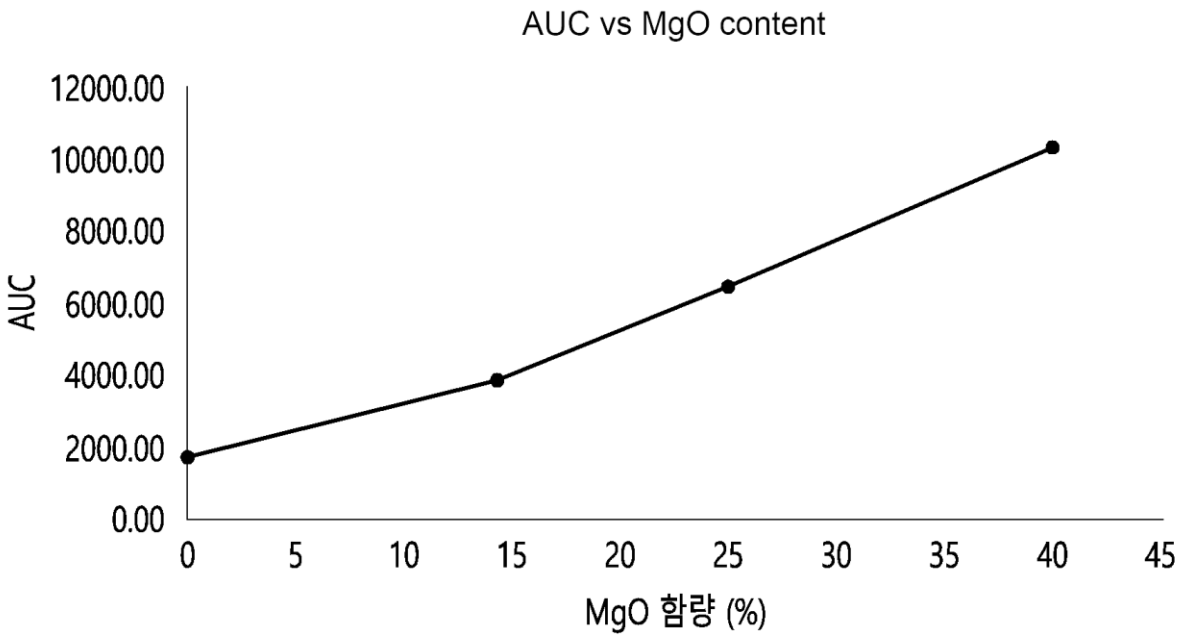

AUC vs MgO content
12000.00
10000.00
8000.00
6000.00
4000.00
2000.00
0.00
AUC
0
5
10
15
20
25
30
35
40
45
MgO 함량 (%)

FIG. 40

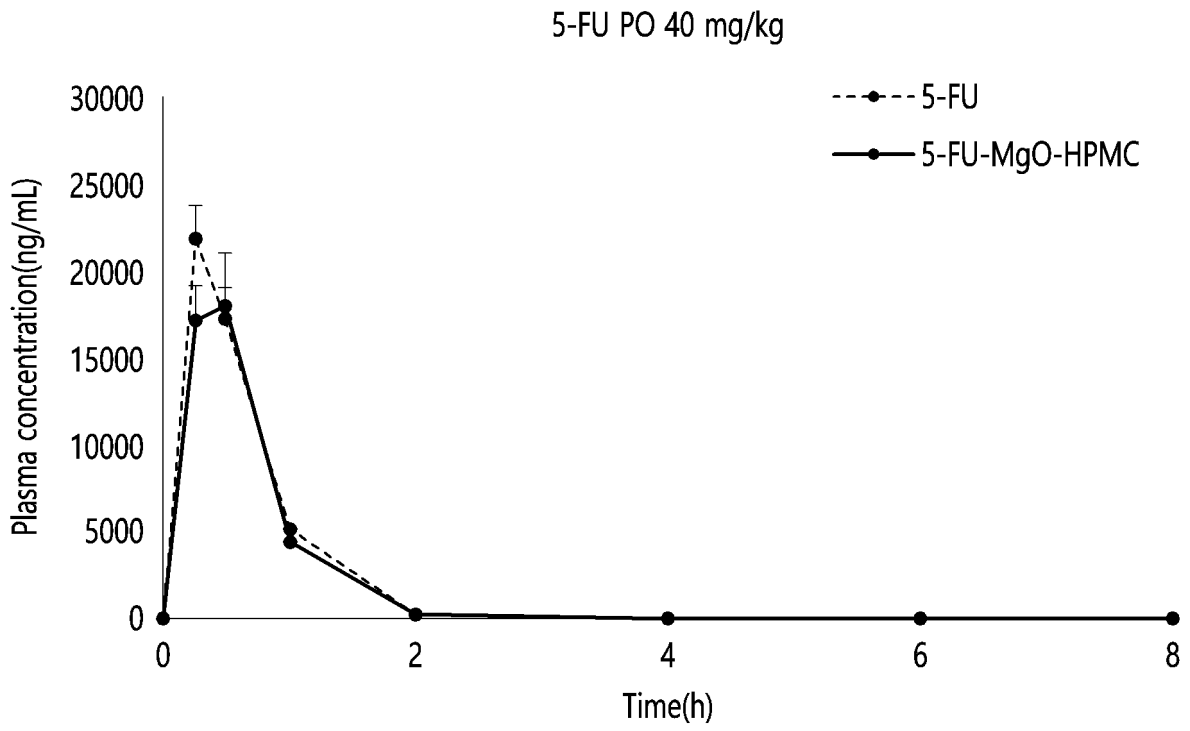

5-FU PO 40 mg/kg
5-FU
5-FU-MgO-HPMC
Plasma concentration(ng/mL)
30000
25000
20000
15000
10000
5000
0
0
2
4
6
8
Time(h)

FIG. 41

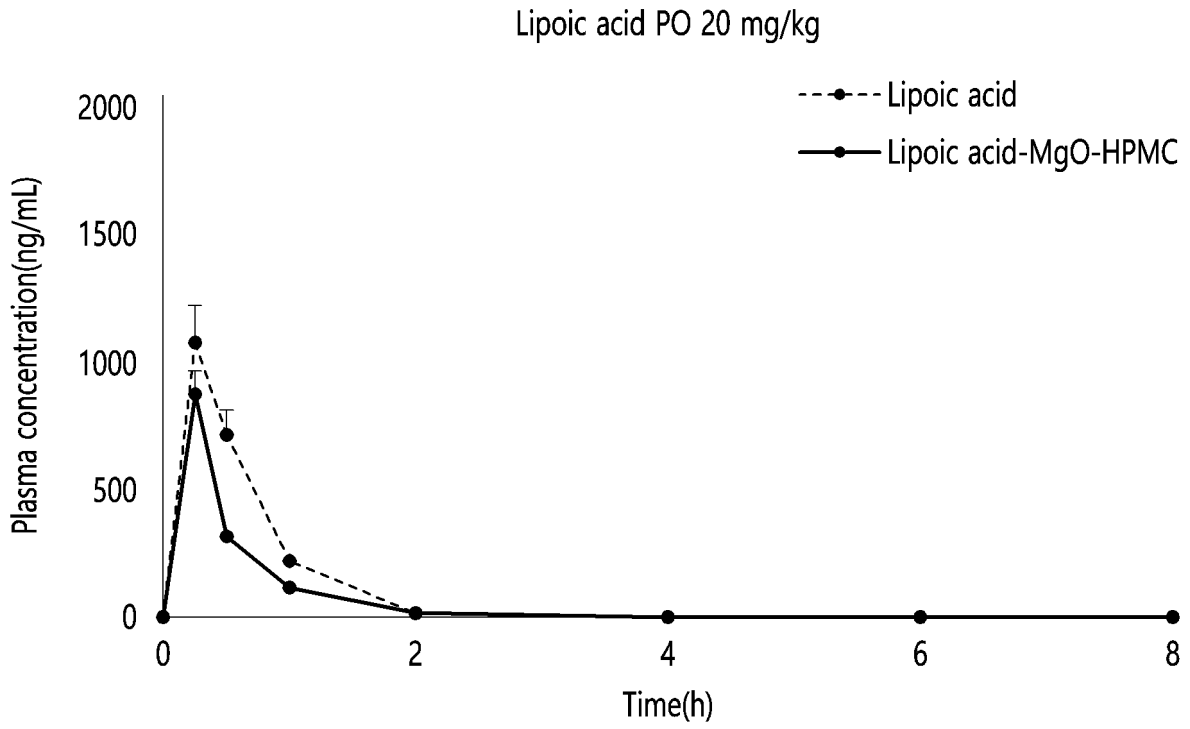

Lipoic acid PO 20 mg/kg
Lipoic acid
Lipoic acid-MgO-HPMC
Plasma concentration(ng/mL)
2000
1500
1000
500
0
0
2
4
6
8
Time(h)

FIG. 42

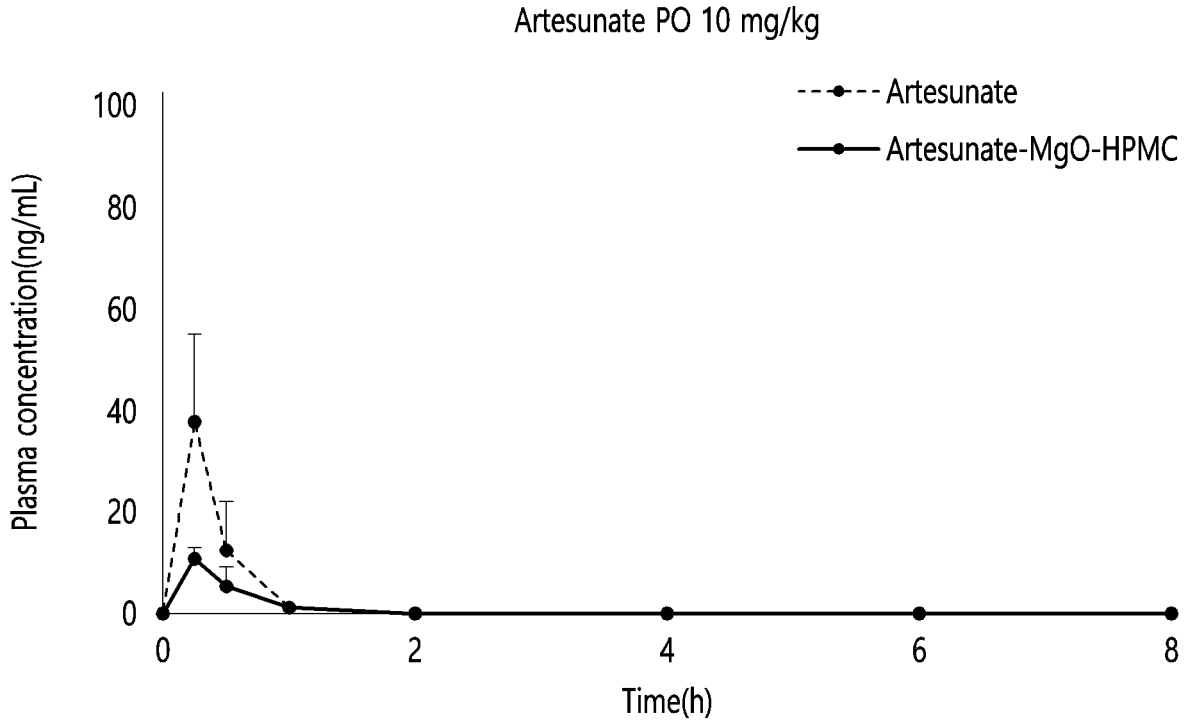

Artesunate PO 10 mg/kg
Artesunate
Artesunate-MgO-HPMC
Plasma concentration(ng/mL)
100
80
60
40
20
0
0
2
4
6
8
Time(h)

FIG. 43

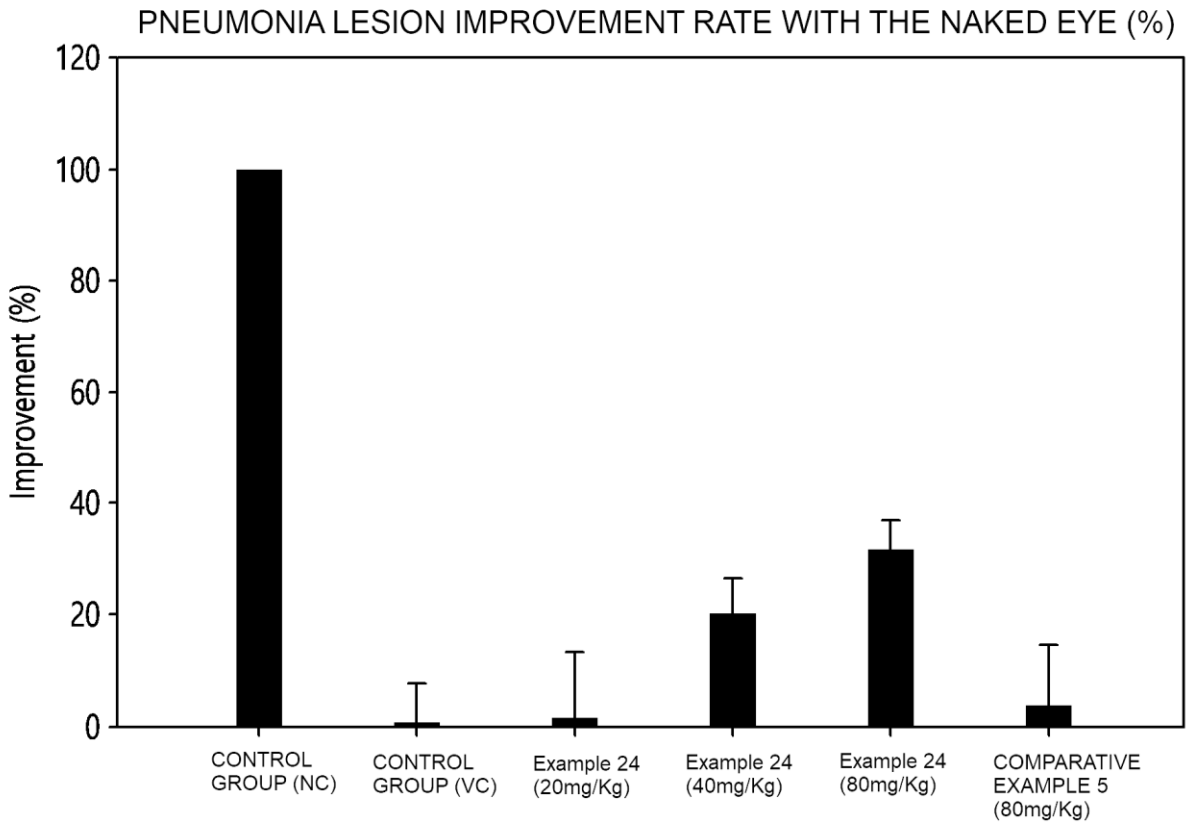

PNEUMONIA LESION IMPROVEMENT RATE WITH THE NAKED EYE (%)
Improvement (%)
120
100
80
60
40
20
0
CONTROL GROUP (NC)
CONTROL GROUP (VC)
Example 24 (20mg/Kg)
Example 24 (40mg/Kg)
Example 24 (80mg/Kg)
COMPARATIVE EXAMPLE 5 (80mg/Kg)

FIG. 44

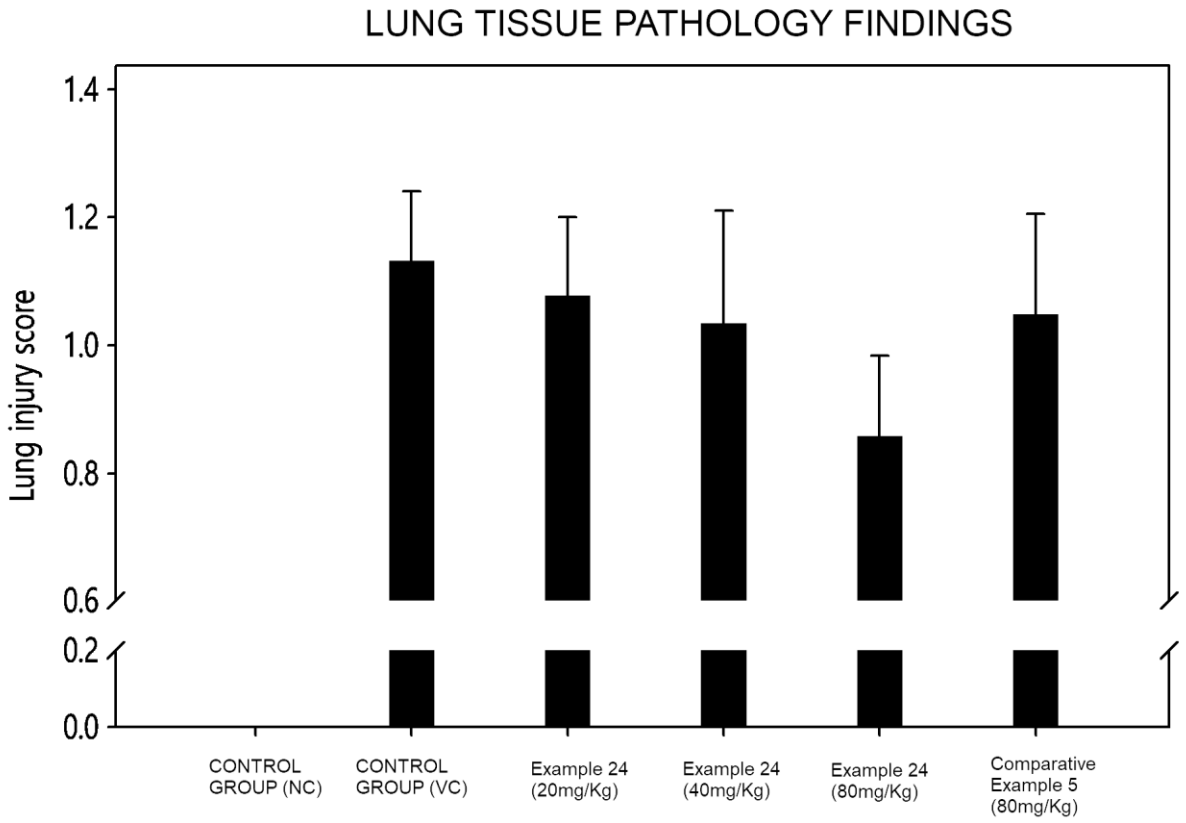

LUNG TISSUE PATHOLOGY FINDINGS
Lung injury score
1.4
1.2
1.0
0.8
0.6
0.2
0.0
CONTROL GROUP (NC)
CONTROL GROUP (VC)
Example 24 (20mg/Kg)
Example 24 (40mg/Kg)
Example 24 (80mg/Kg)
Comparative Example 5 (80mg/Kg)

FIG. 45

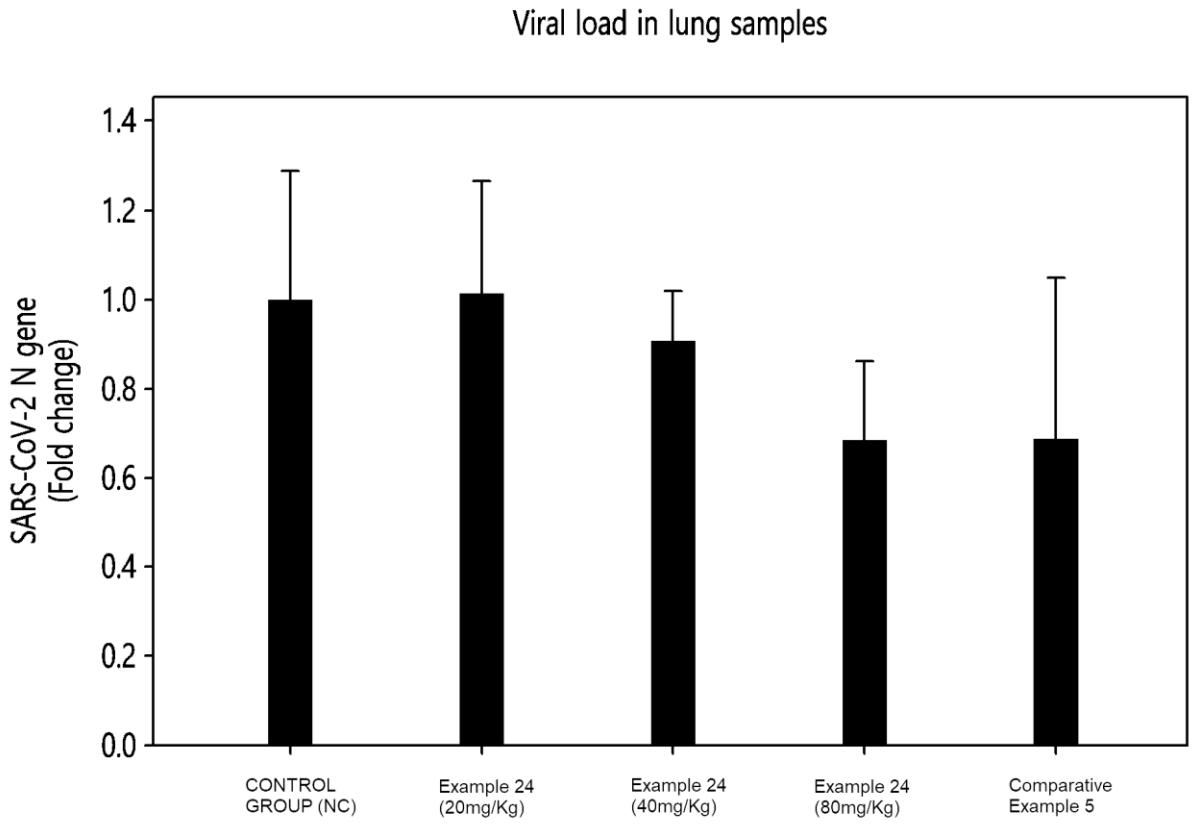

Viral load in lung samples
SARS-CoV-2 N gene
(Fold change)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
CONTROL GROUP (NC)
Example 24 (20mg/Kg)
Example 24 (40mg/Kg)
Example 24 (80mg/Kg)
Comparative Example 5

FIG. 46

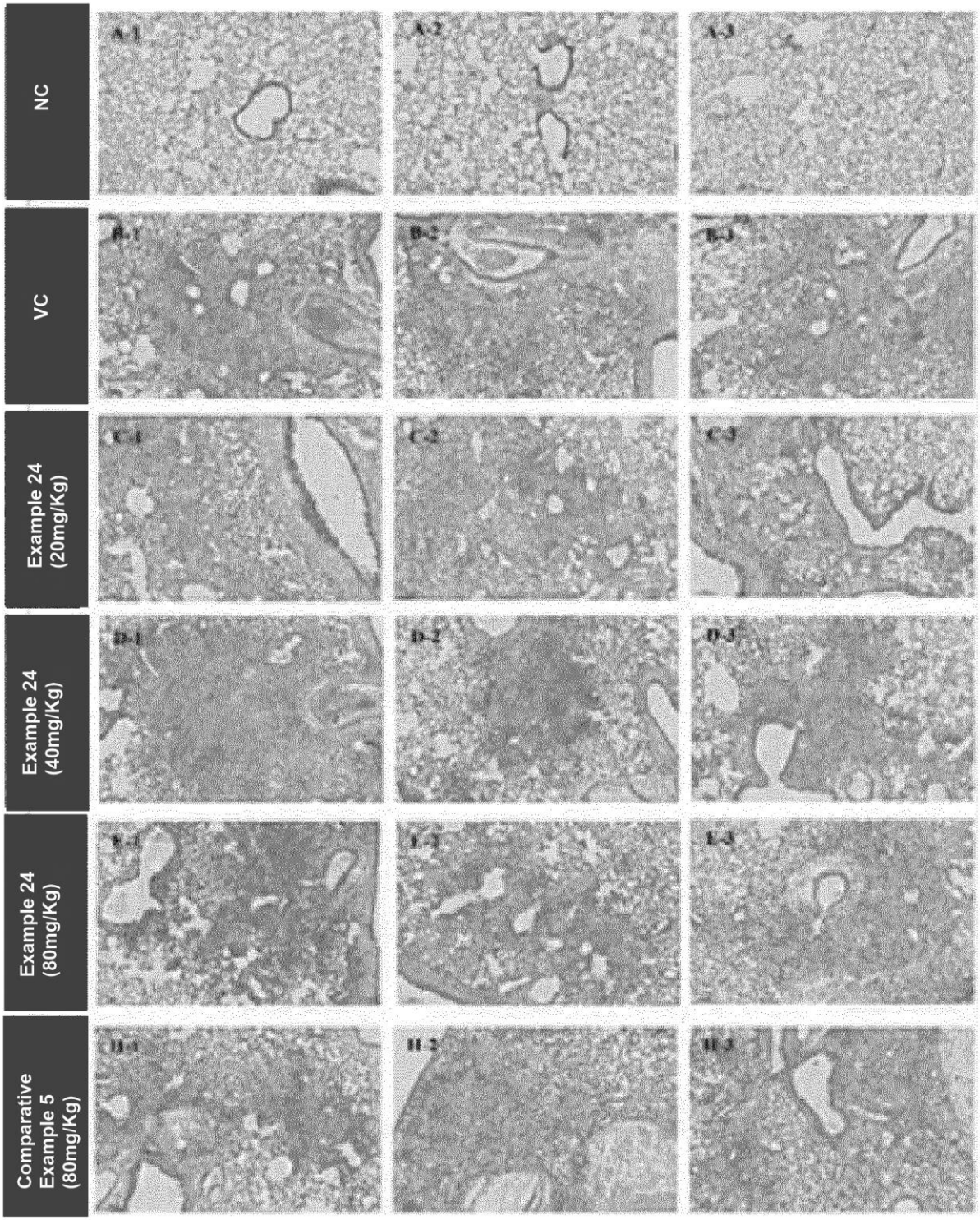

NC
VC
Example 24 (20mg/Kg)
Example 24 (40mg/Kg)
Example 24 (80mg/Kg)
Comparative Example 5 (80mg/Kg)

FIG. 47