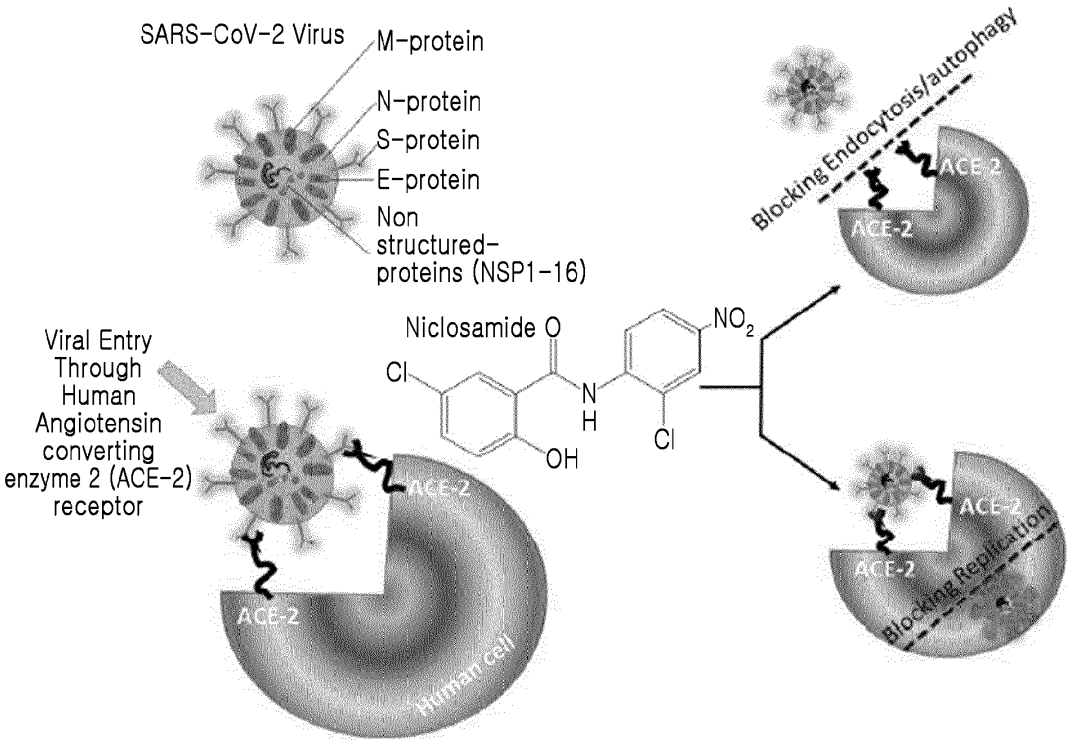
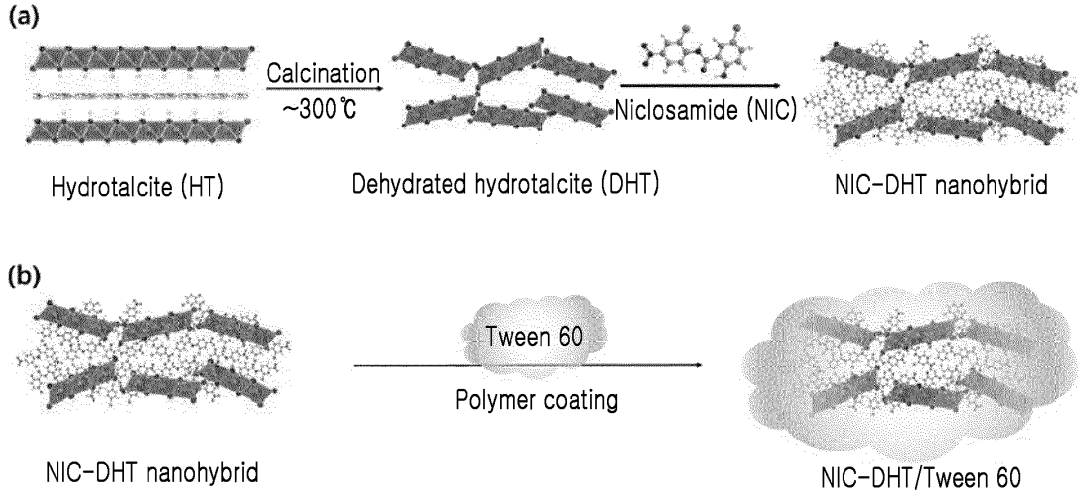
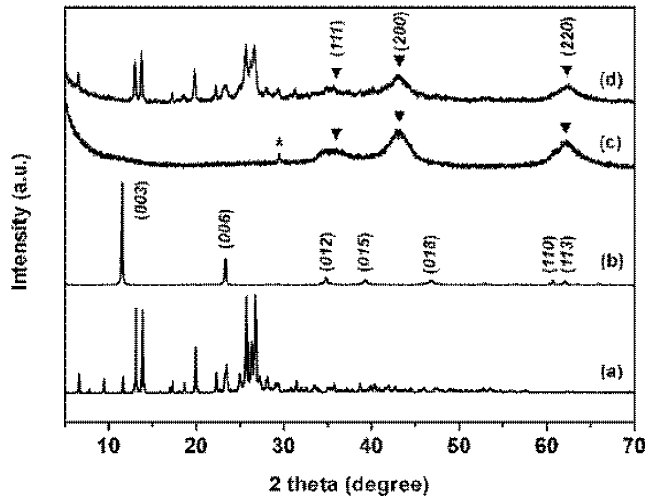
[도1]


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

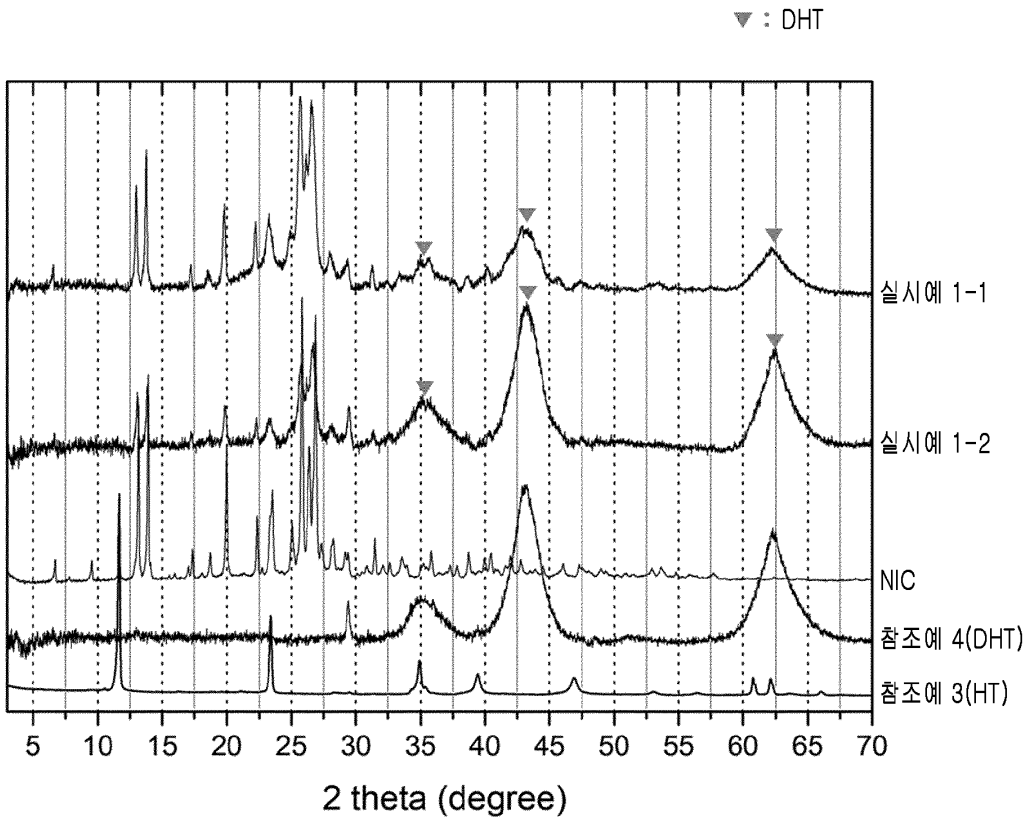
[도2]


(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

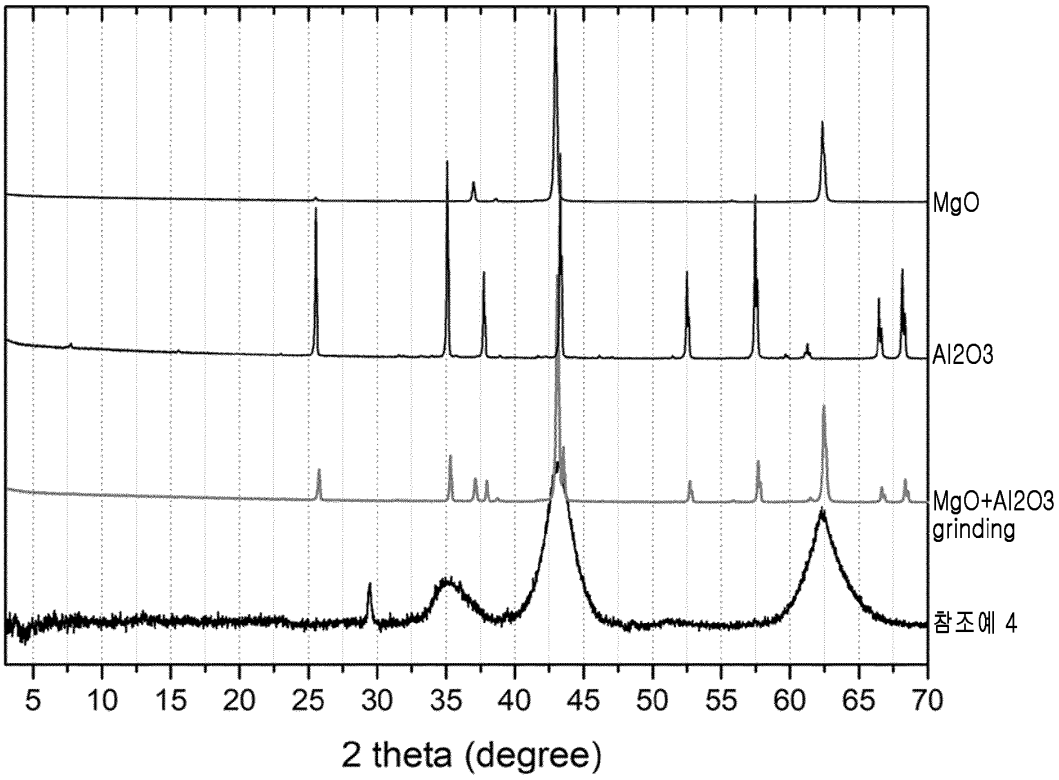
[도3]


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

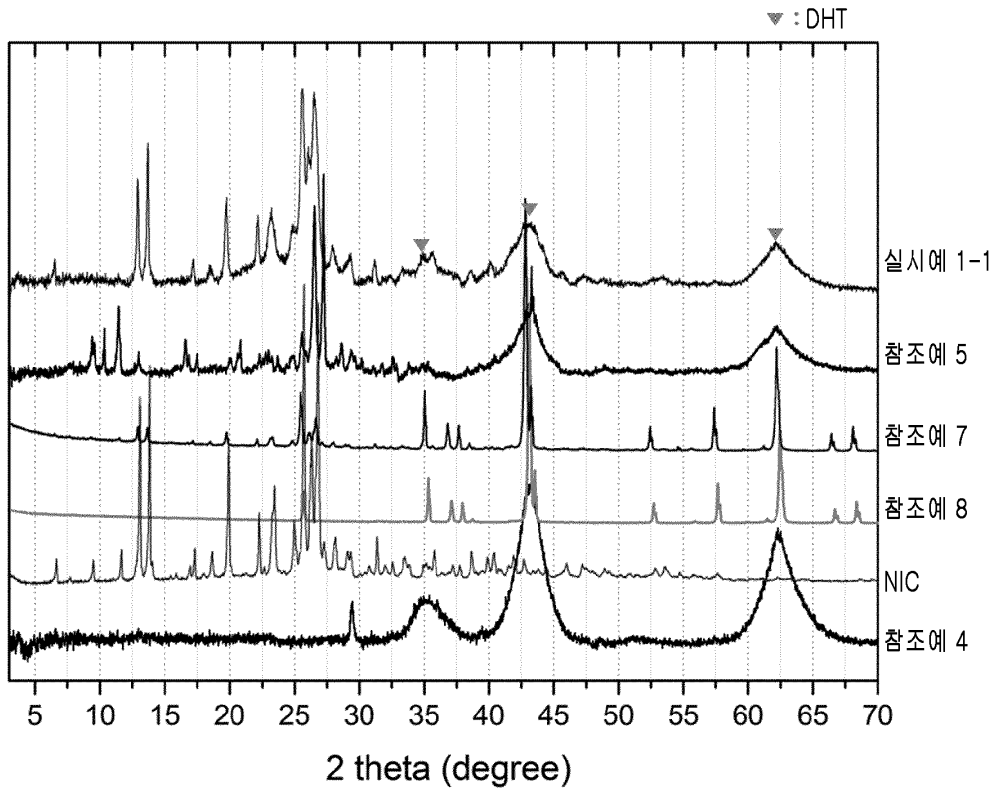
[도4]


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

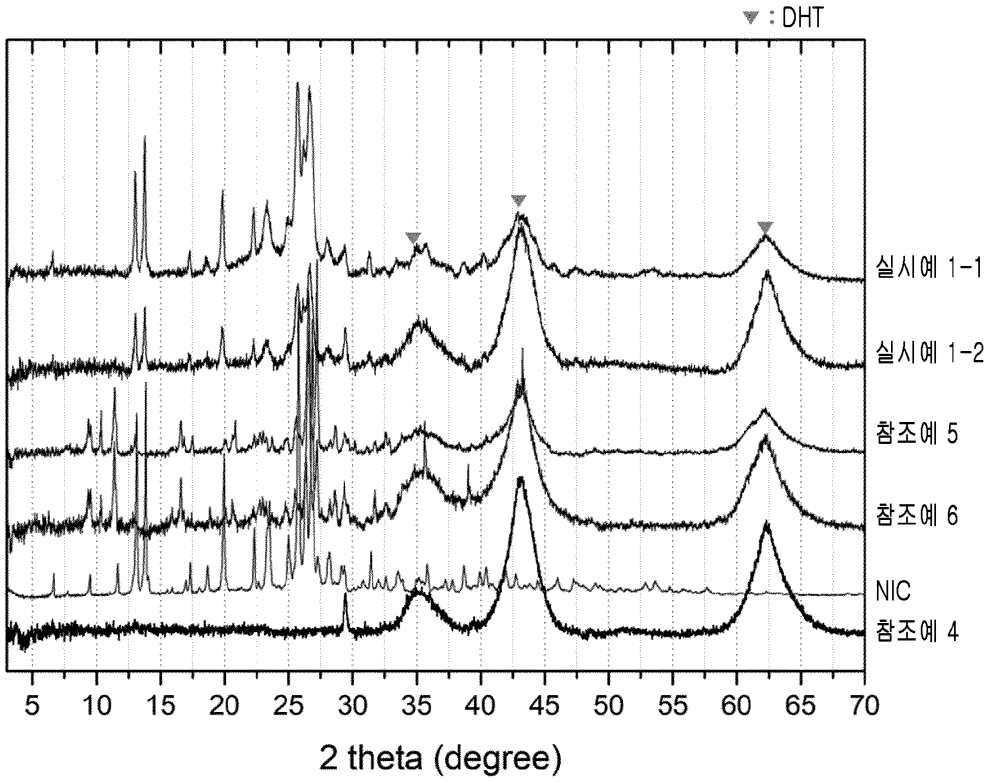
[도5]


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

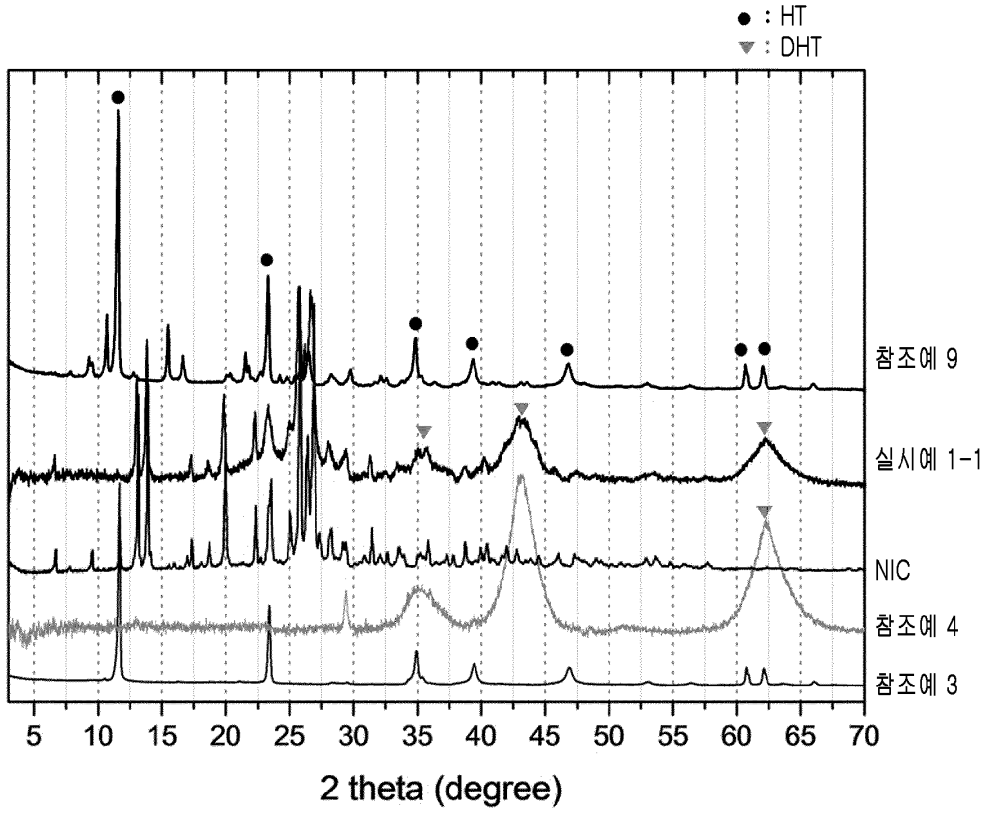
[도6]


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

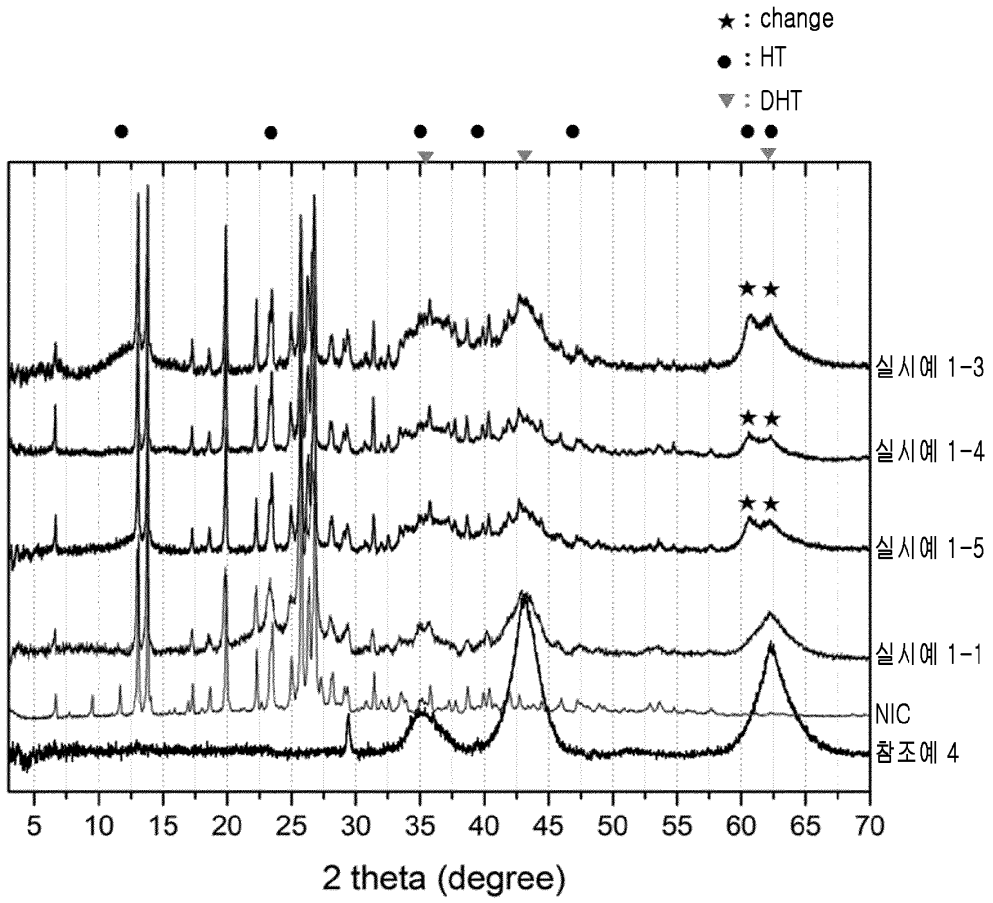
[도7]


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

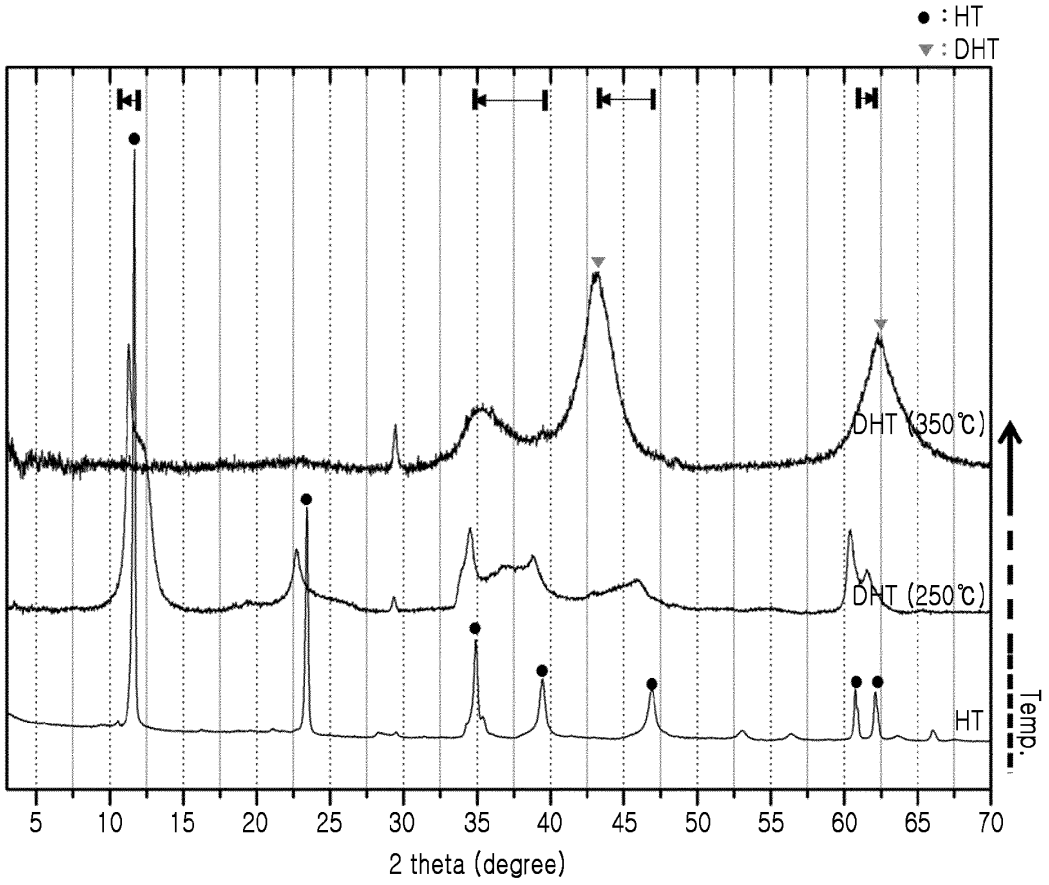
[도8]


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

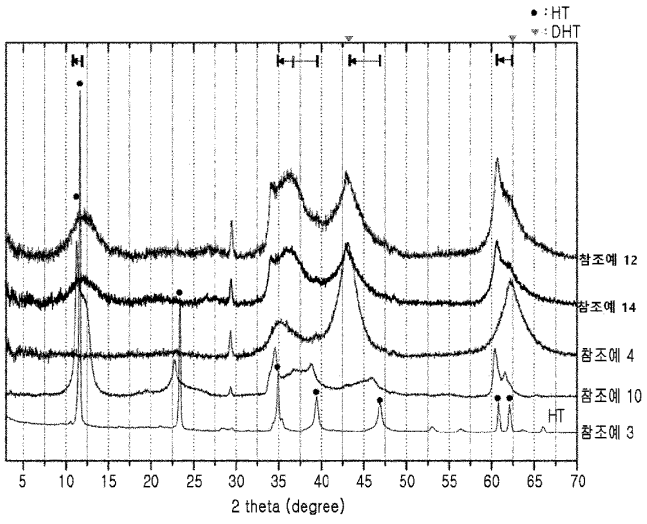
[도9]


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

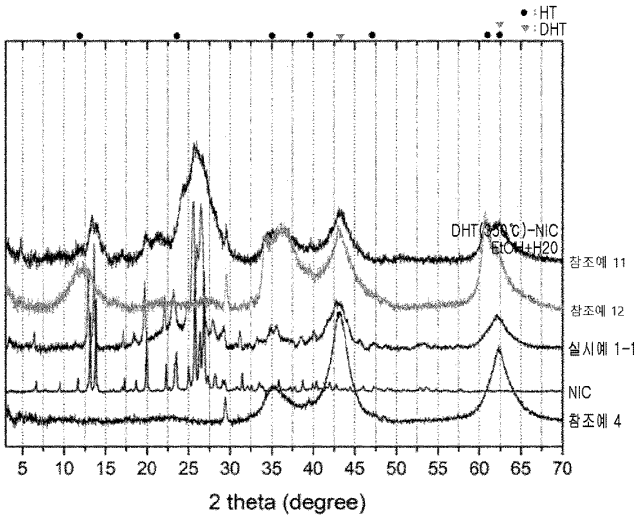
[도10]


● : 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)

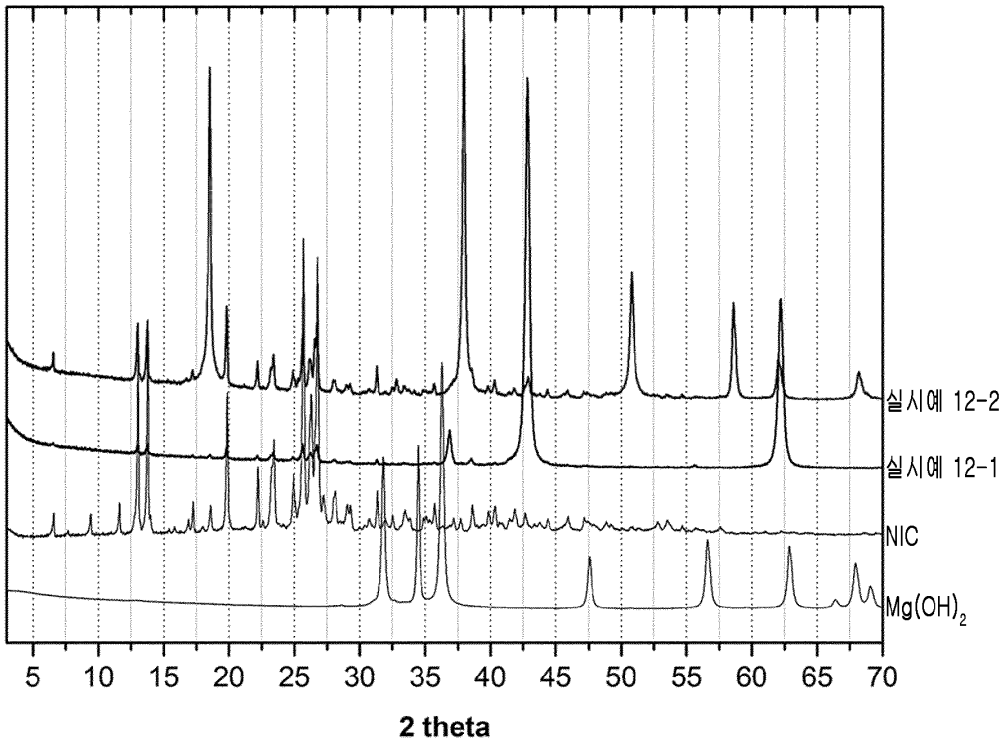
[도11]


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

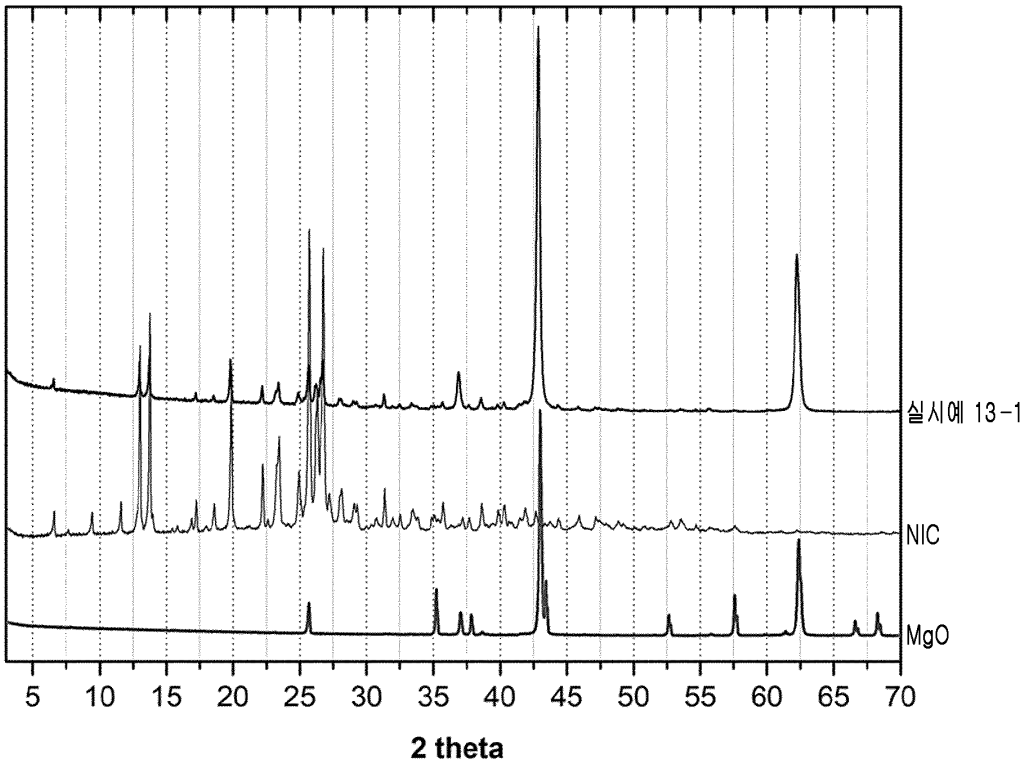
[도12]


● : HT
▽ : DHT
DHT(350℃)-NIC
EtOH+H2O
참조예 11
참조예 12
실시예 1-1
NIC
참조예 4
5 10 15 20 25 30 35 40 45 50 55 60 65 70
2 theta (degree)

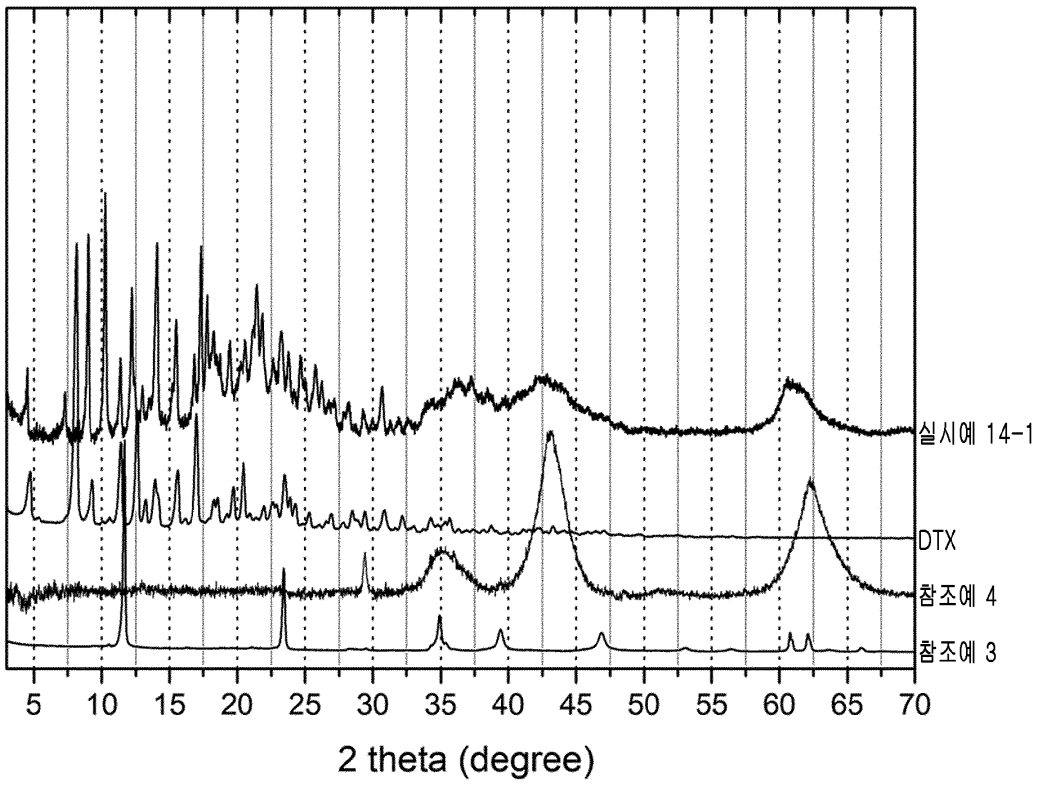
[도13]


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

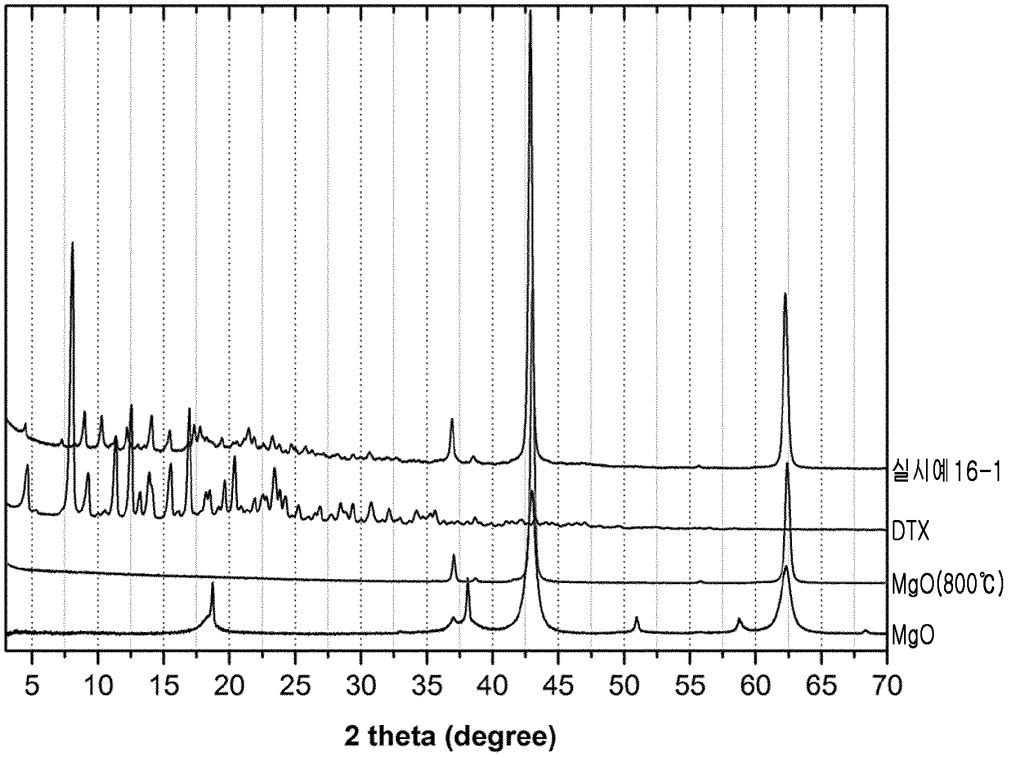
[도14]


실시예 13-1
NIC
MgO
5 10 15 20 25 30 35 40 45 50 55 60 65 70
2 theta

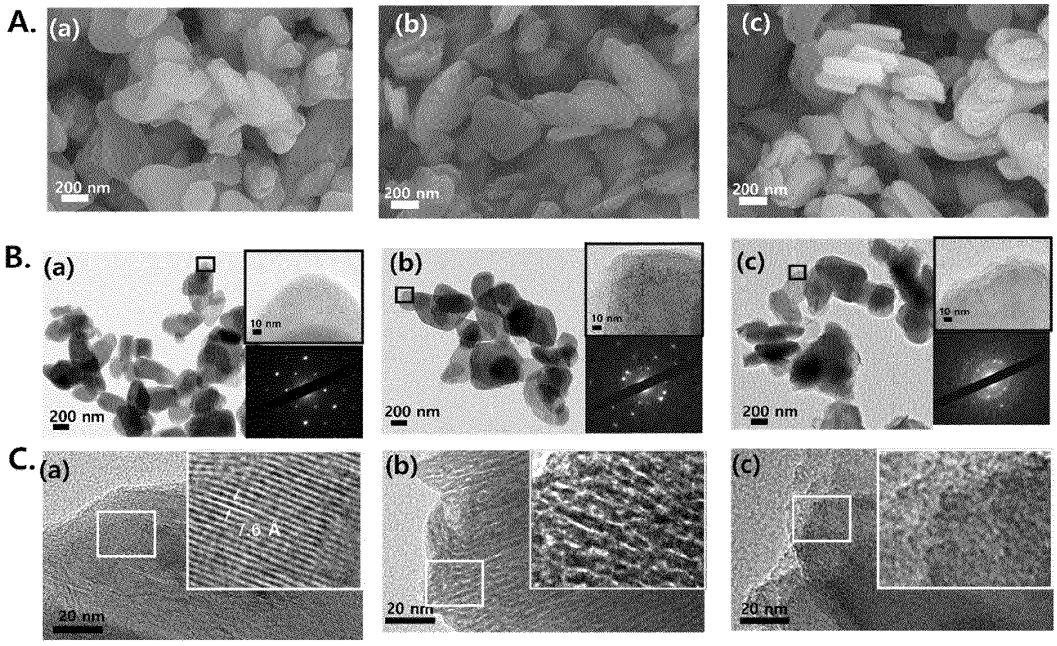
[도15]


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

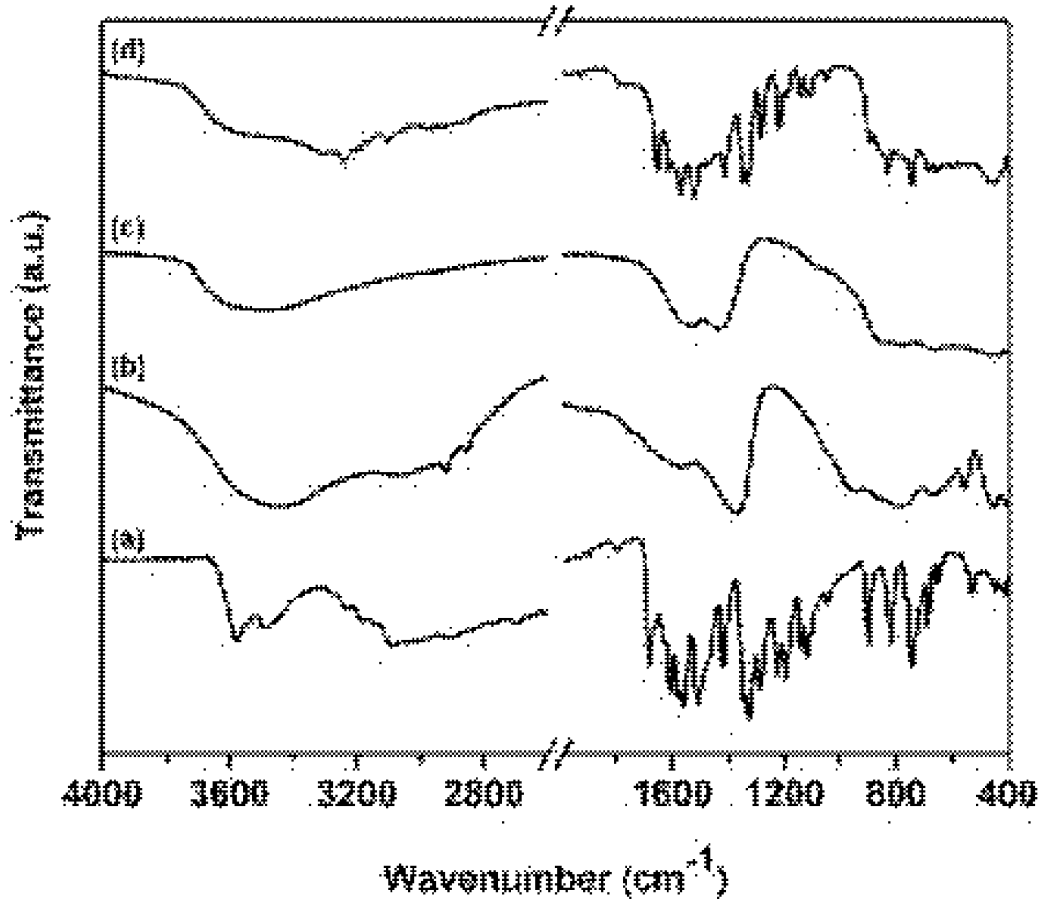
[도16]


실시예16-1
DTX
MgO(800℃)
MgO
5 10 15 20 25 30 35 40 45 50 55 60 65 70
2 theta (degree)

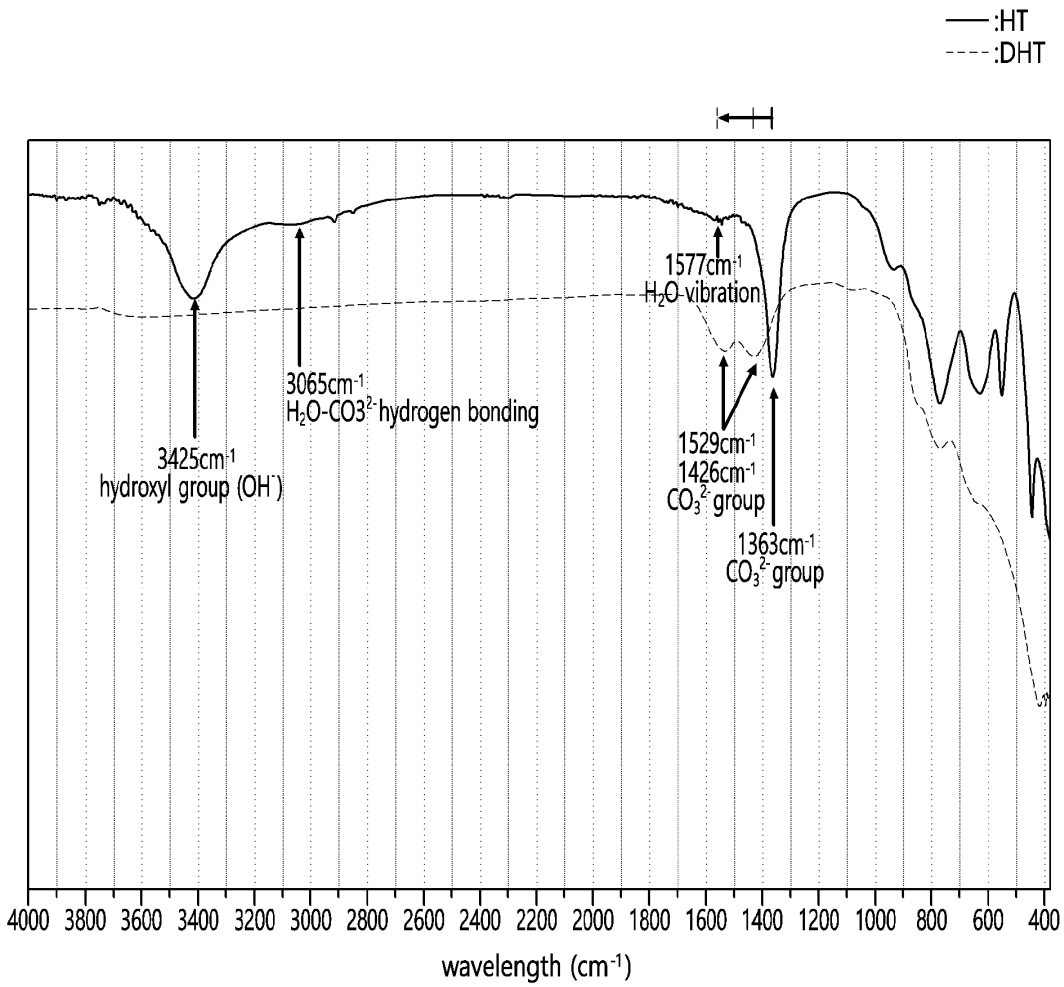
[도17]


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

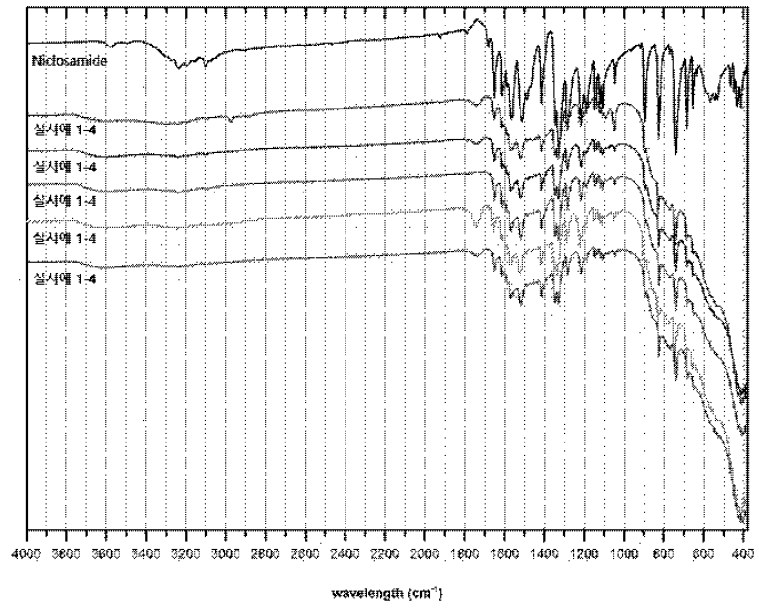
[도18]


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

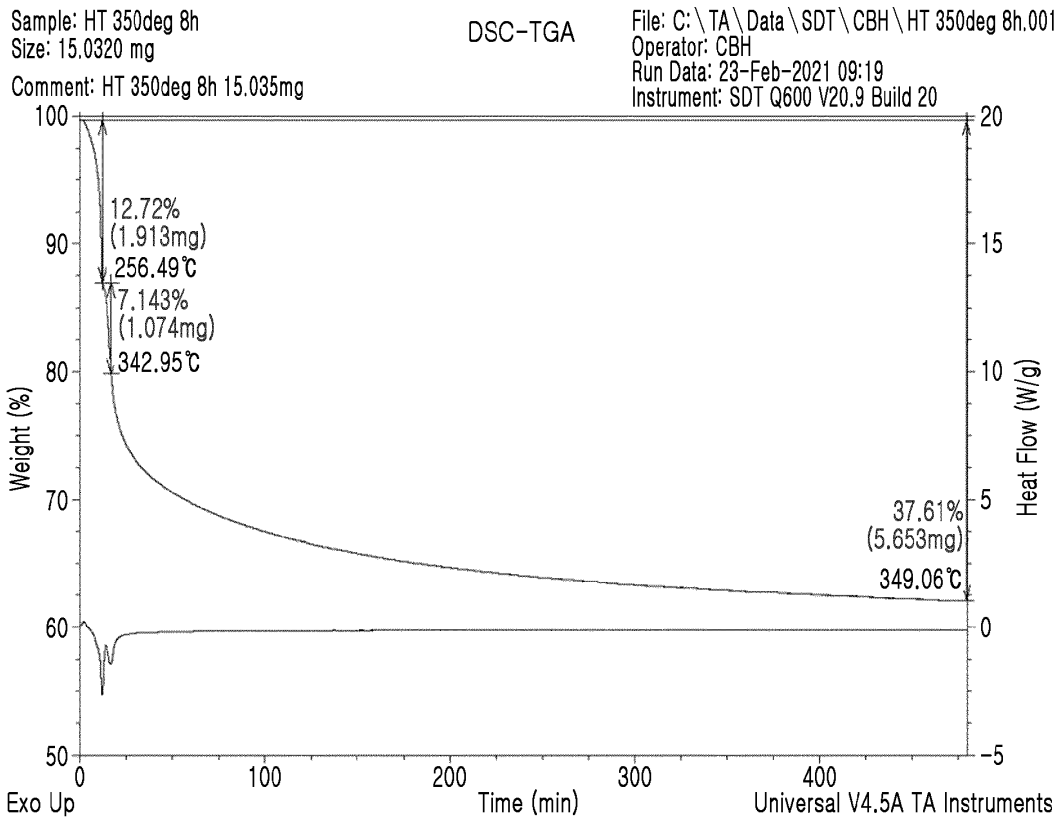
[도19]


:HT
:DHT
1577cm-1
H2O vibration
3065cm-1
H2O-CO32- hydrogen bonding
3425cm-1
hydroxyl group (OH-)
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)

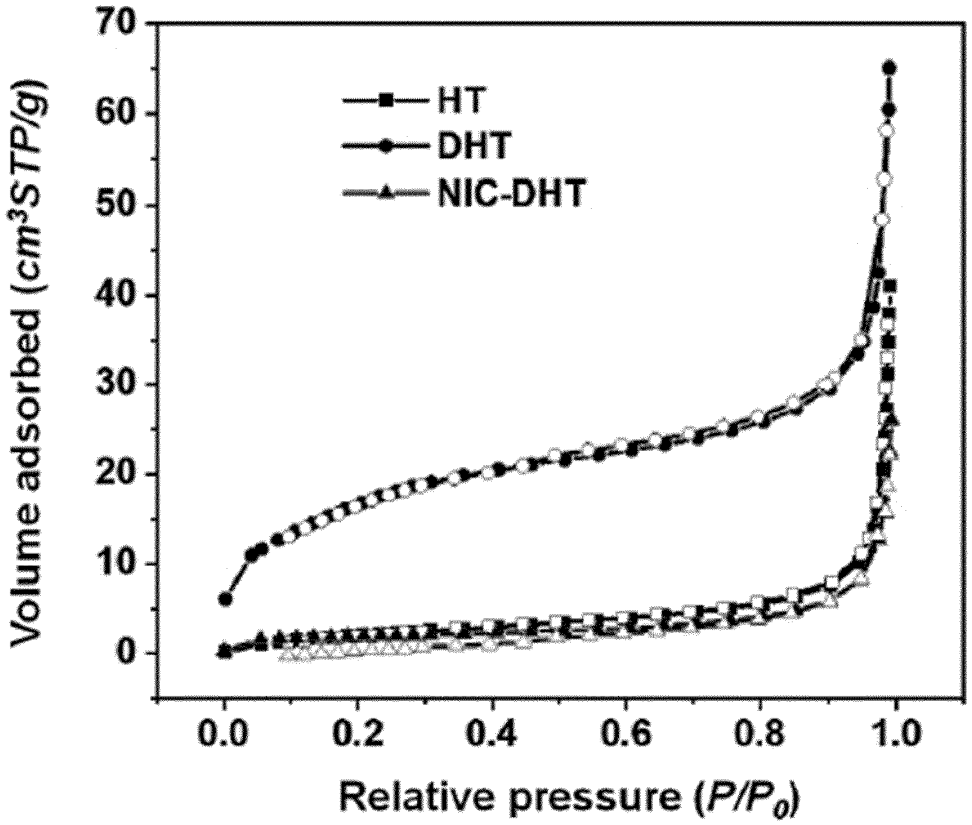
[도20]


Niclosamide
실시예 1-4
실시예 1-4
실시예 1-4
실시예 1-4
실시예 1-4
wavelength (cm-1)

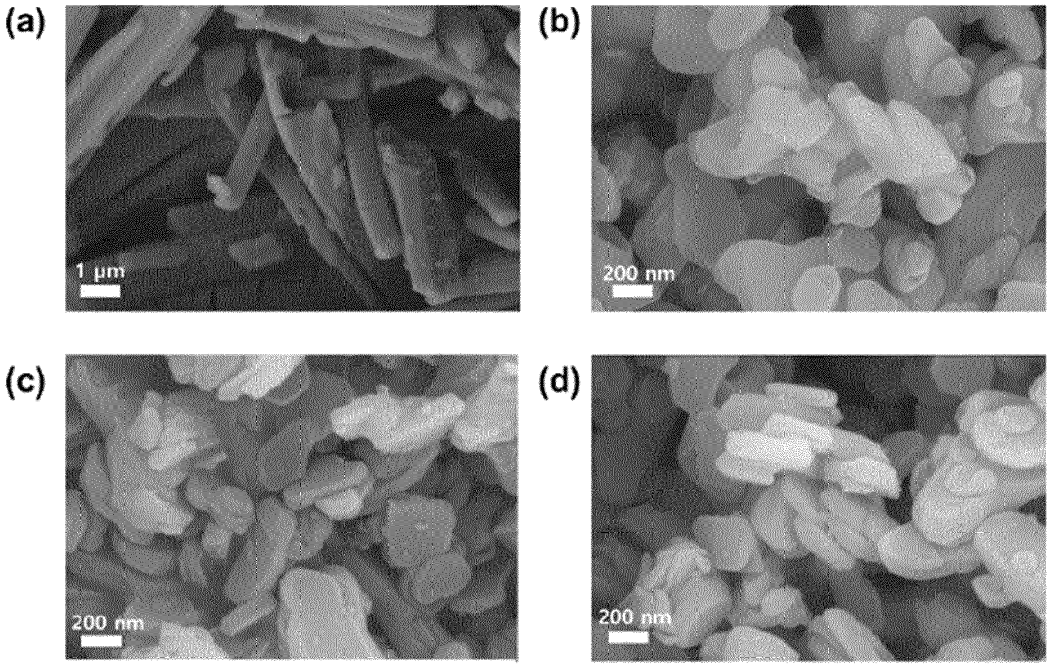
[도21]


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

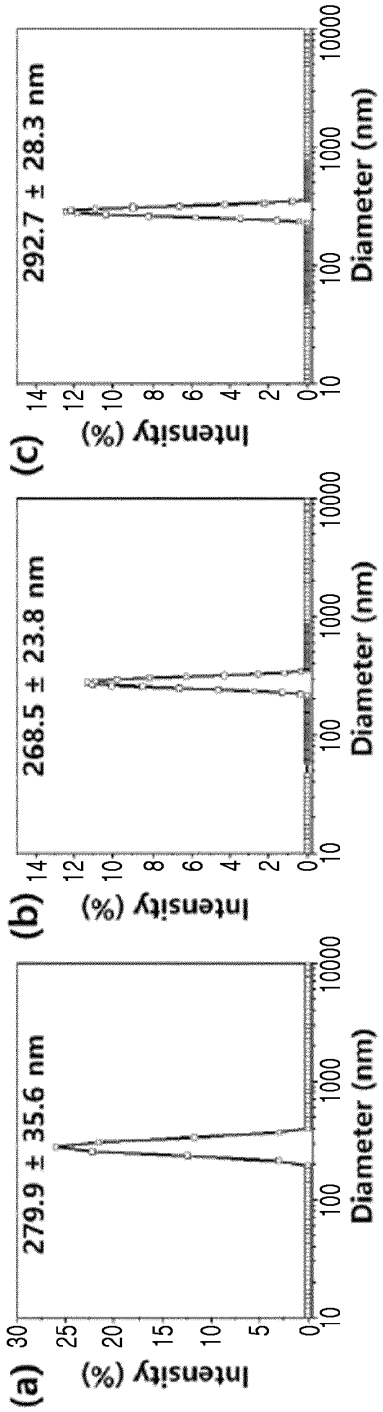
[도22]


HT
DHT
NIC-DHT
Volume adsorbed (cm³STP/g)
Relative pressure (P/P0)

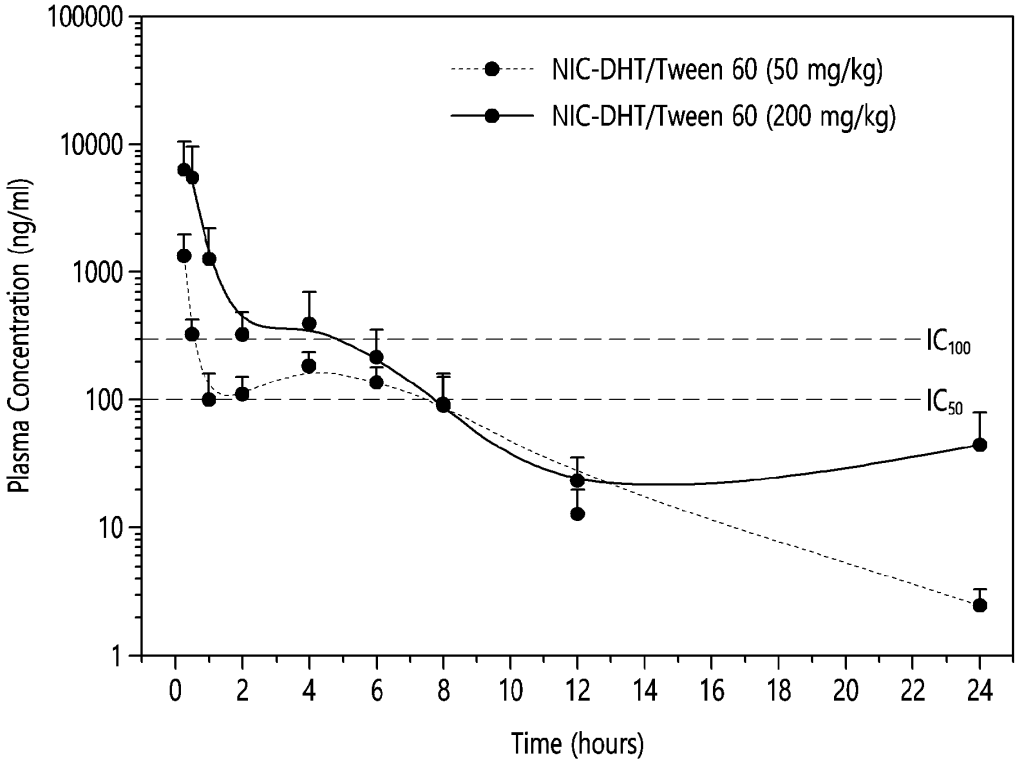
[도23]



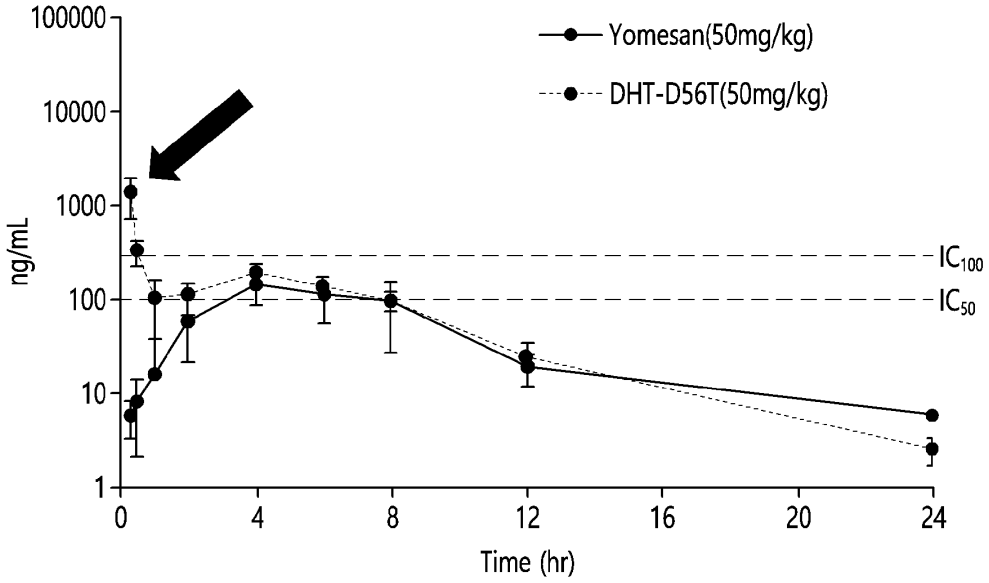
[도24]


(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)

[도25]

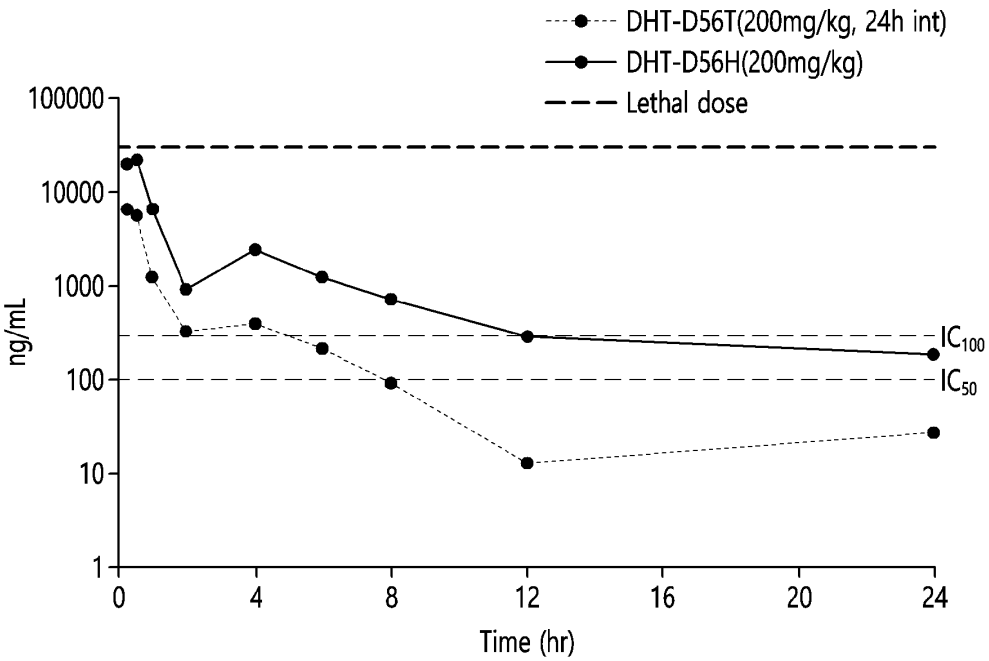

NIC-DHT/Tween 60 (50 mg/kg)
NIC-DHT/Tween 60 (200 mg/kg)
IC100
IC50
Plasma Concentration (ng/ml)
Time (hours)
100000
10000
1000
100
10
1
0
2
4
6
8
10
12
14
16
18
20
22
24

[도26]



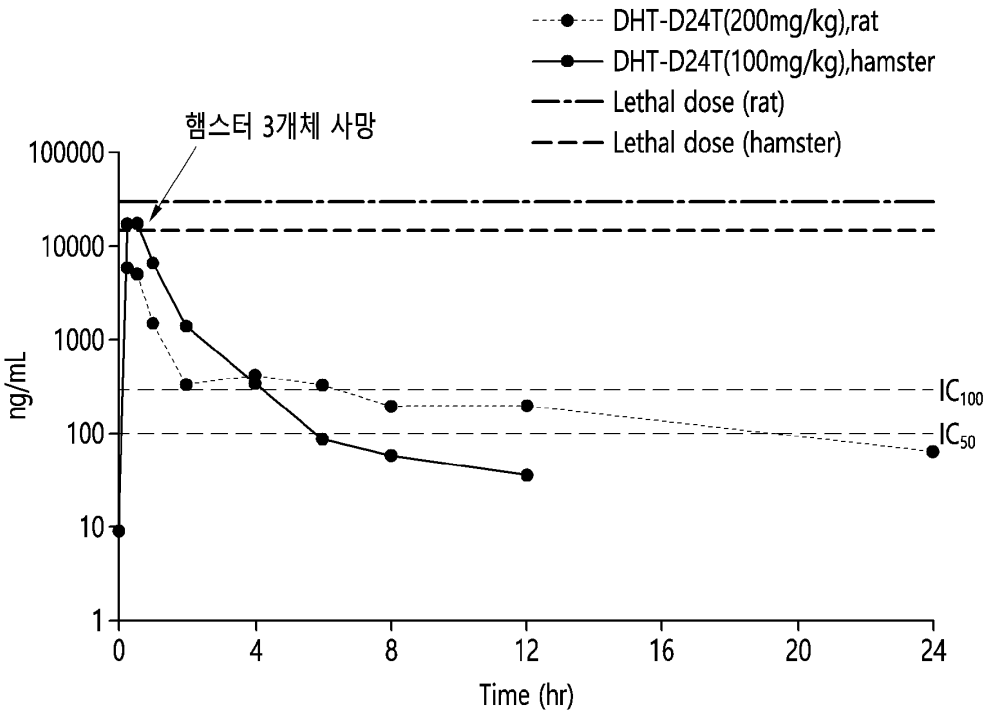
제형화 효과			
	Cmax	AUC	note
Yomesan	142.7	1096.8	제형화 결과, Cmax 9.5배 ↑ AUC 1.7배 ↑
실시예 9 (DHT-D56T)	1350.3	1823.8	

[도27]



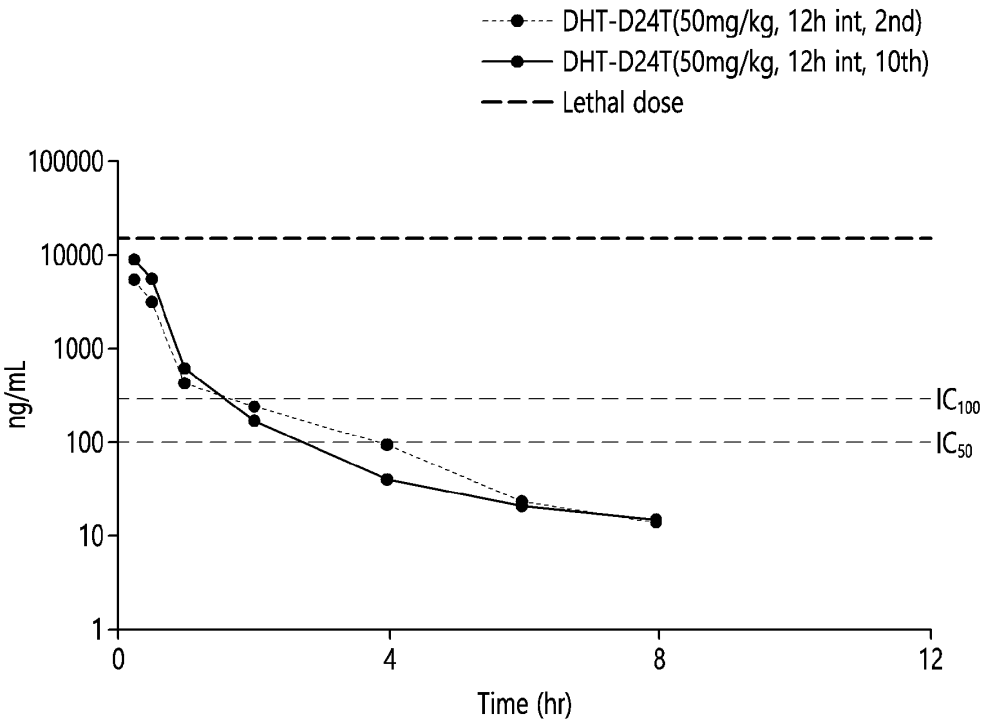
부형제 효과				
샘플명	부형제	Cmax	AUC	note
실시예 9 DHT-D56T	Tween60	5481.4	6819.3	부형제를 HPMC로 교환하여, Cmax 3.9배 ↑ AUC 4.7배 ↑
실시예 6 DHT-D56H	HPMC	21547.6	31863.5	

[도28]



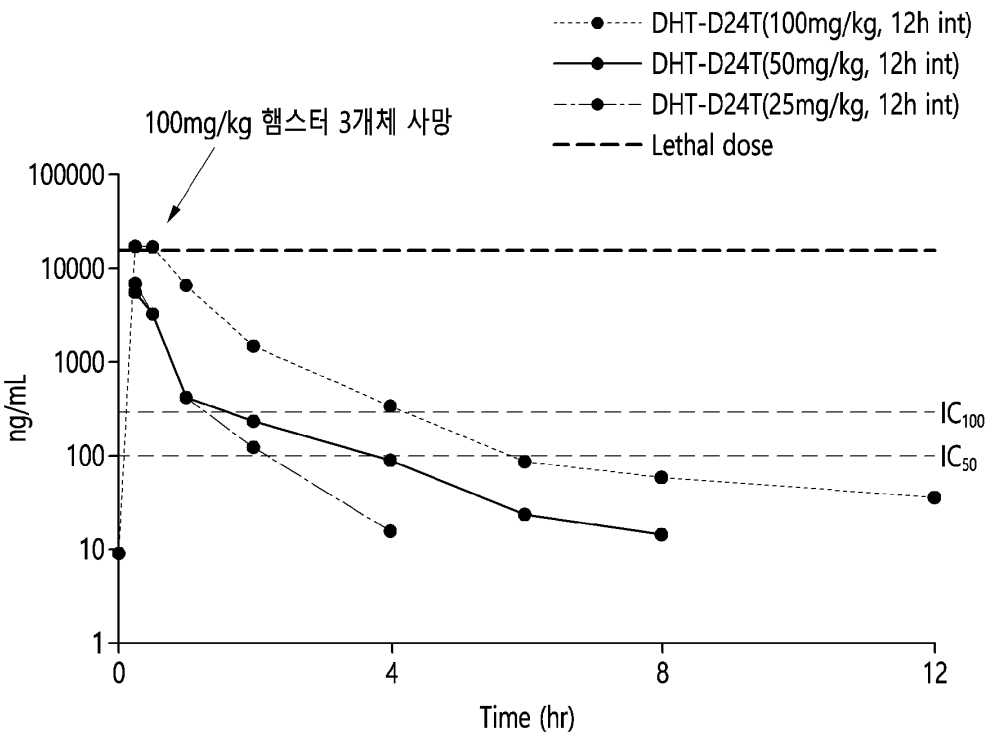
종간 차이				
동물모델	용량 (mg/kg)	Cmax	AUC	Note
Rat	200	5883.1	8935.0	잦은 간격으로 용량을 나누어 투여하는 것이 AUC ↑
Hamster	100	16843.5	18425.0	

[도29]



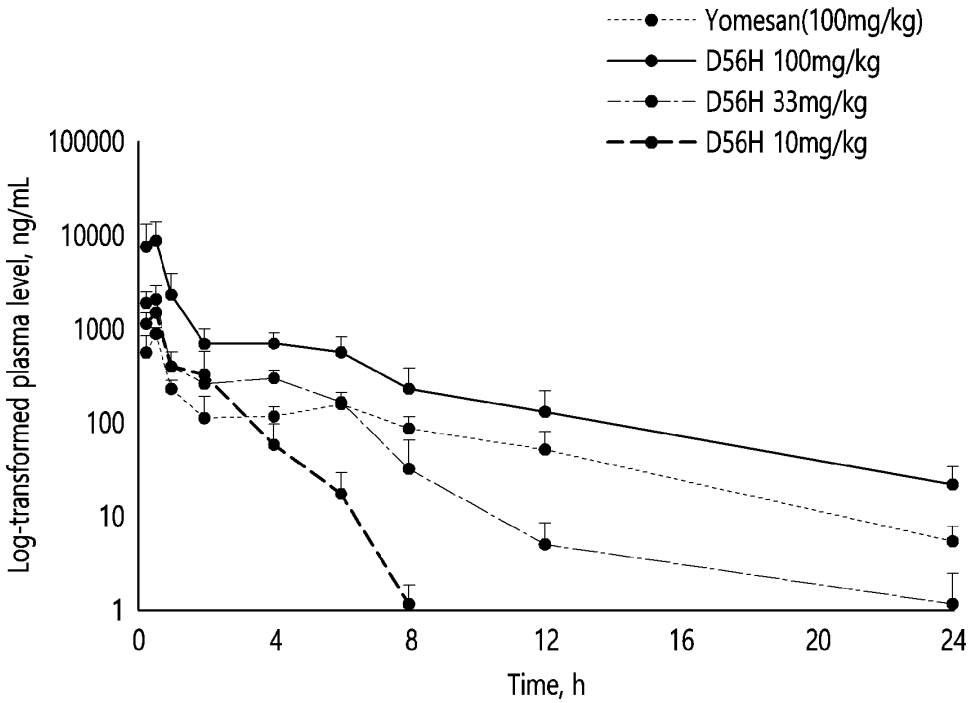
용량 차이		
투여횟수	Cmax	AUC
2	5372.3	3431.3
10	8746.3	5102.5

[도30]



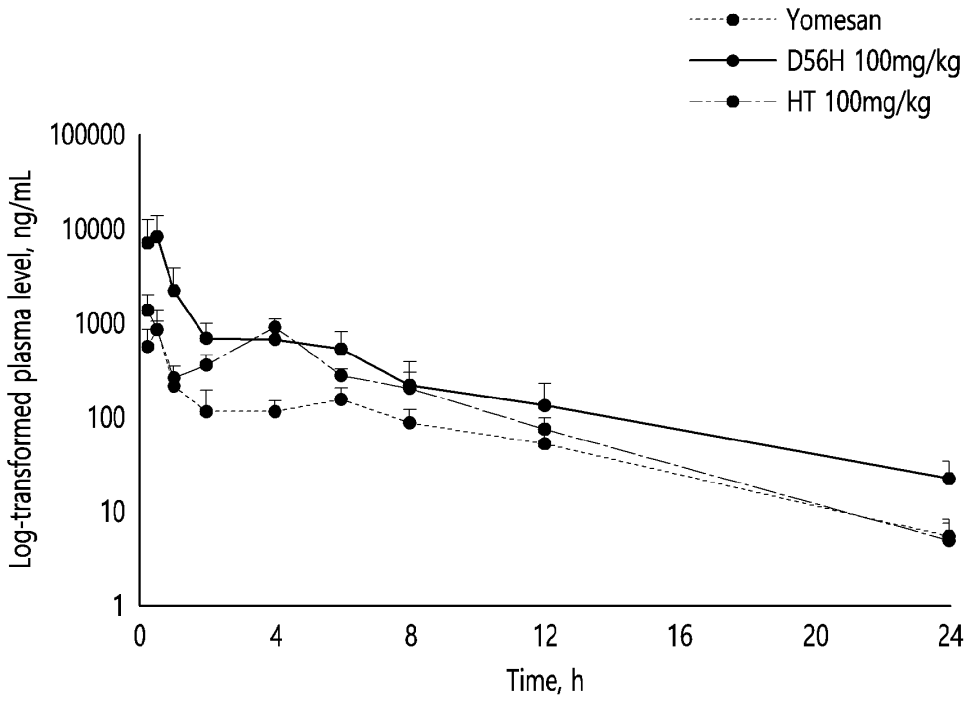
용량 차이		
용량(mg/kg)	Cmax	AUC
25	6803.7	3381.7
50	5372.3	3431.3
100	16843.5	18425.0

[도31]



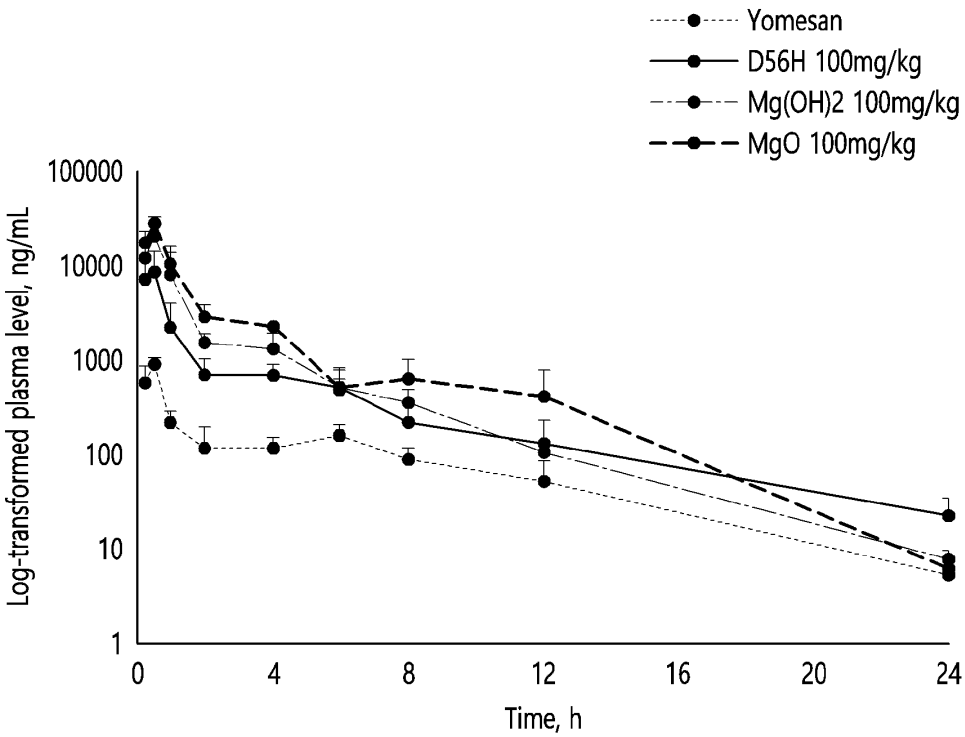
PK Parameters	Niclosamide, PO			
	Yomesan	D56H		
	100 mg/kg	100 mg/kg	33 mg/kg	10 mg/kg
AUC(last)	2010.85	11599.26	2939.11	1702.92
Cmax	868.84	8078.23	2308.47	1542.97
Tmax	0.50	0.50	0.50	0.50
$t_{1/2}$	4.15	4.02	3.03	0.77

[도32]



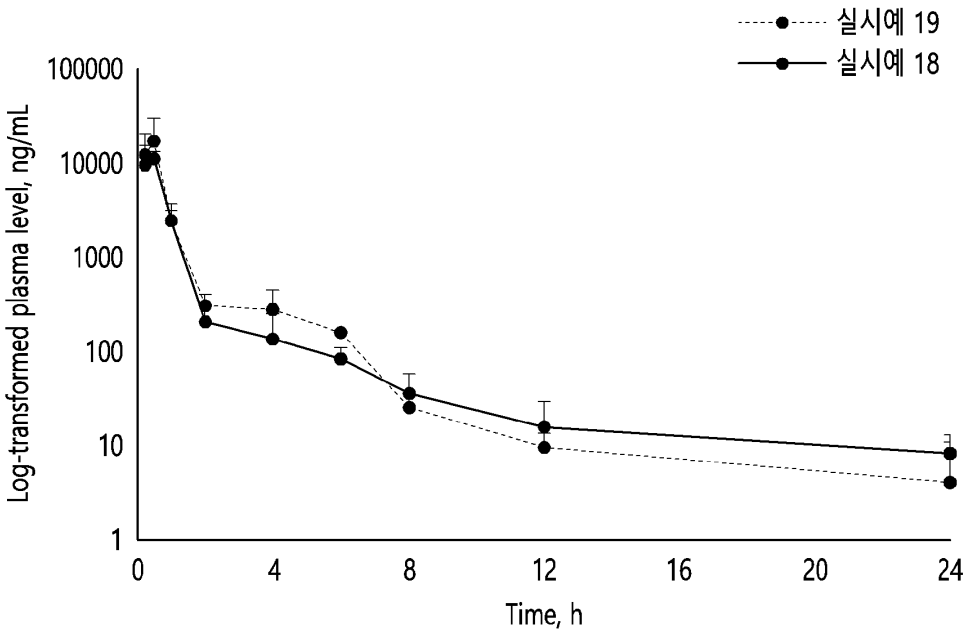
PK Parameters	Niclosamide, PO		
	Yomesan	D56H	HT
	100 mg/kg	100 mg/kg	100 mg/kg
AUC(last)	2010.85	11599.26	4919.93
Cmax	868.84	8078.23	1487.80
Tmax	0.50	0.50	0.25
$t_{1/2}$	4.15	4.02	3.06

[도33]



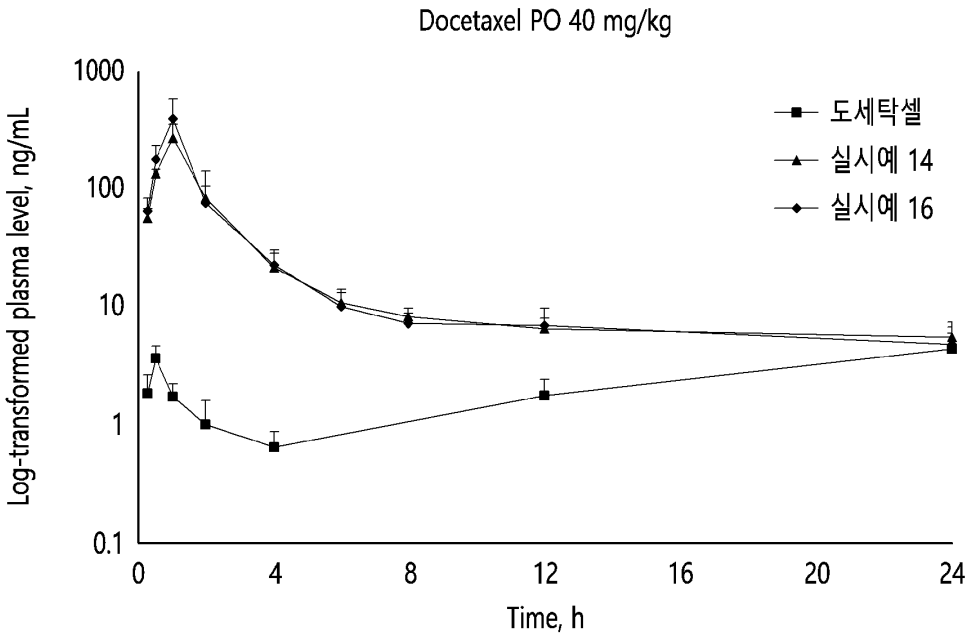
PK Parameters	Niclosamide, PO			
	Yomesan	D56H	Mg(OH)2	MgO
	100 mg/kg	100 mg/kg	100 mg/kg	100 mg/kg
AUC(last)	2010.85	11599.26	22437.26	33797.23
Cmax	868.84	8078.23	17828.61	21438.78
Tmax	0.50	0.50	0.50	0.50
$t_{1/2}$	4.15	4.02	2.67	2.37

[도34]

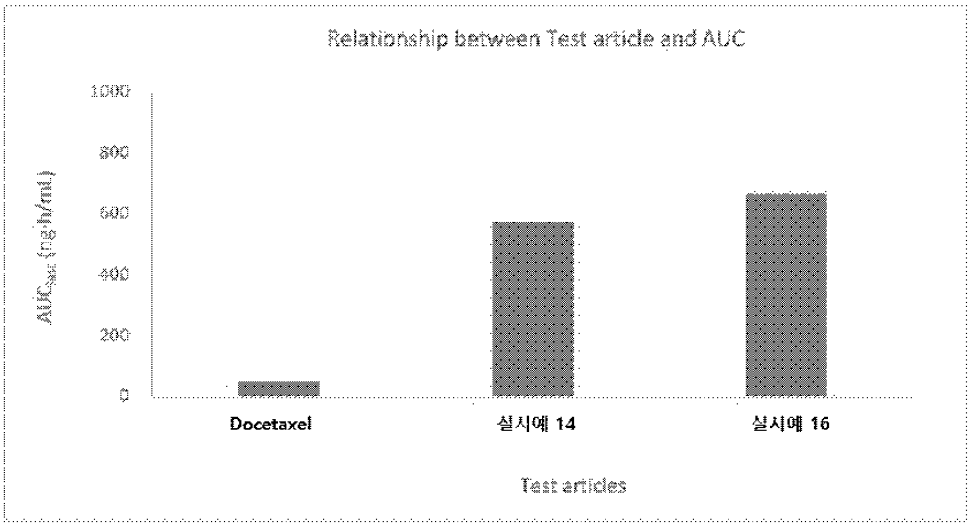


PK Parameters	Niclosamide PO 100 mg/kg	
	실시예 19	실시예 18
AUC(last)	17206.82	18311.94
Cmax	14805.71	17694.34
Tmax	0.50	0.50
$t_{1/2}$	17.36	8.20

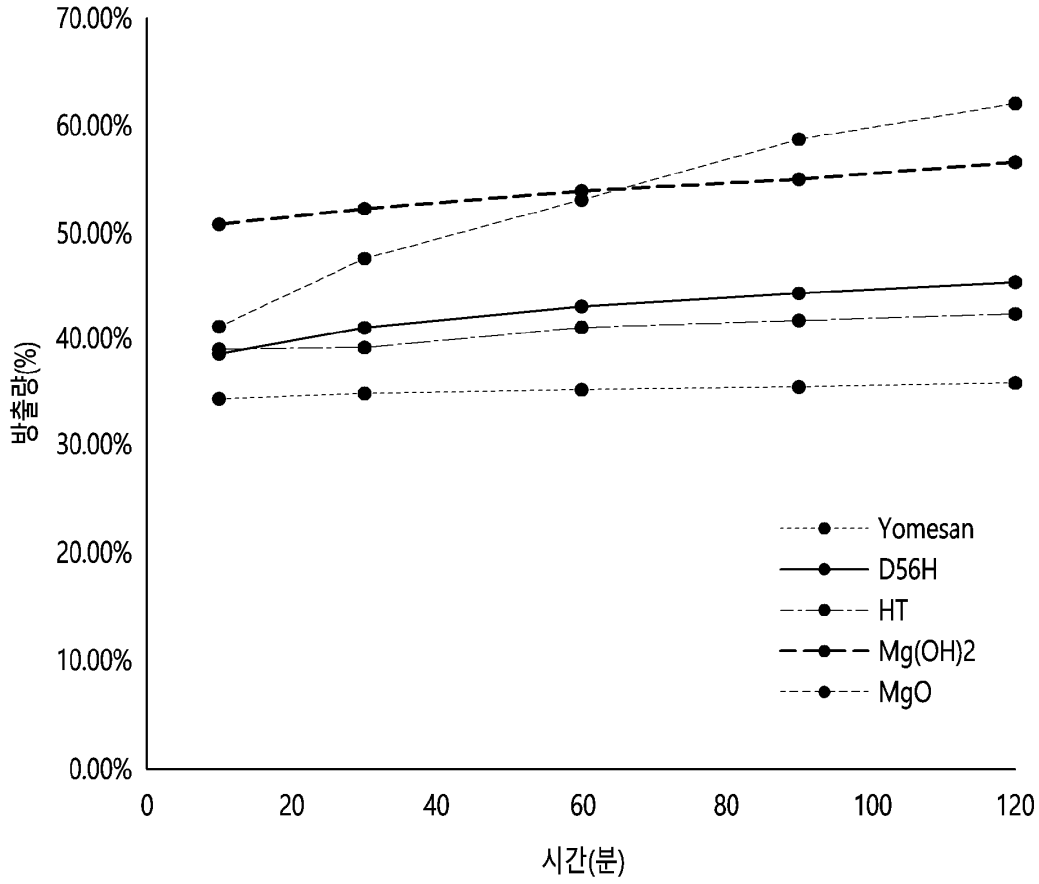
[도35]


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
도세탁셀
실시예 14
실시예 16

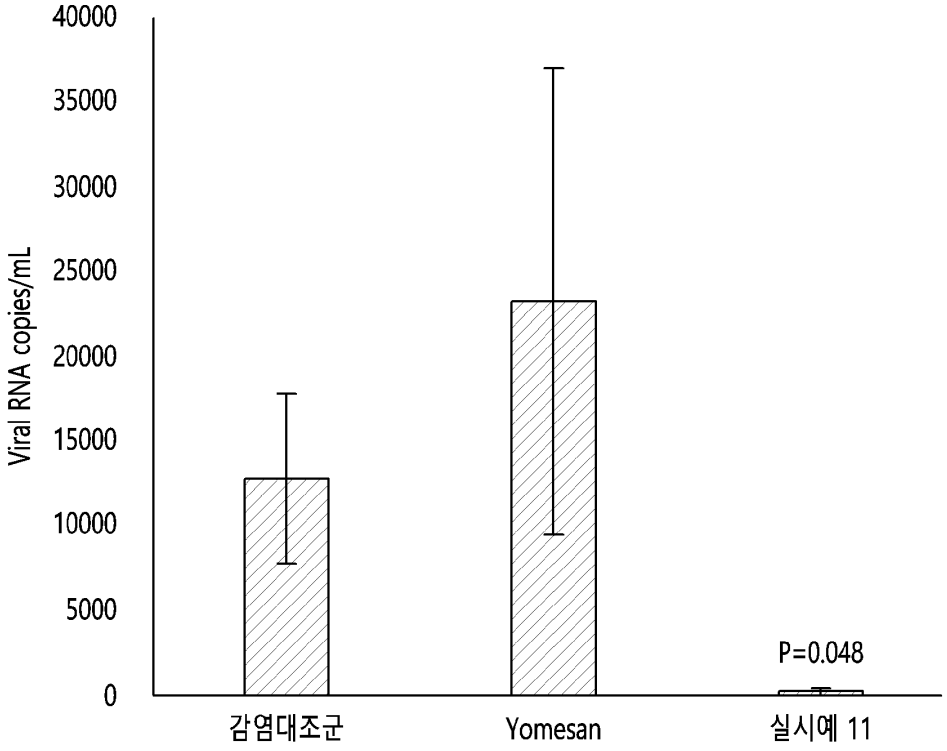
[도36]


Relationship between Test article and AUC
1000
800
600
400
200
0
Docetaxel
실시예 14
실시예 16
Test articles

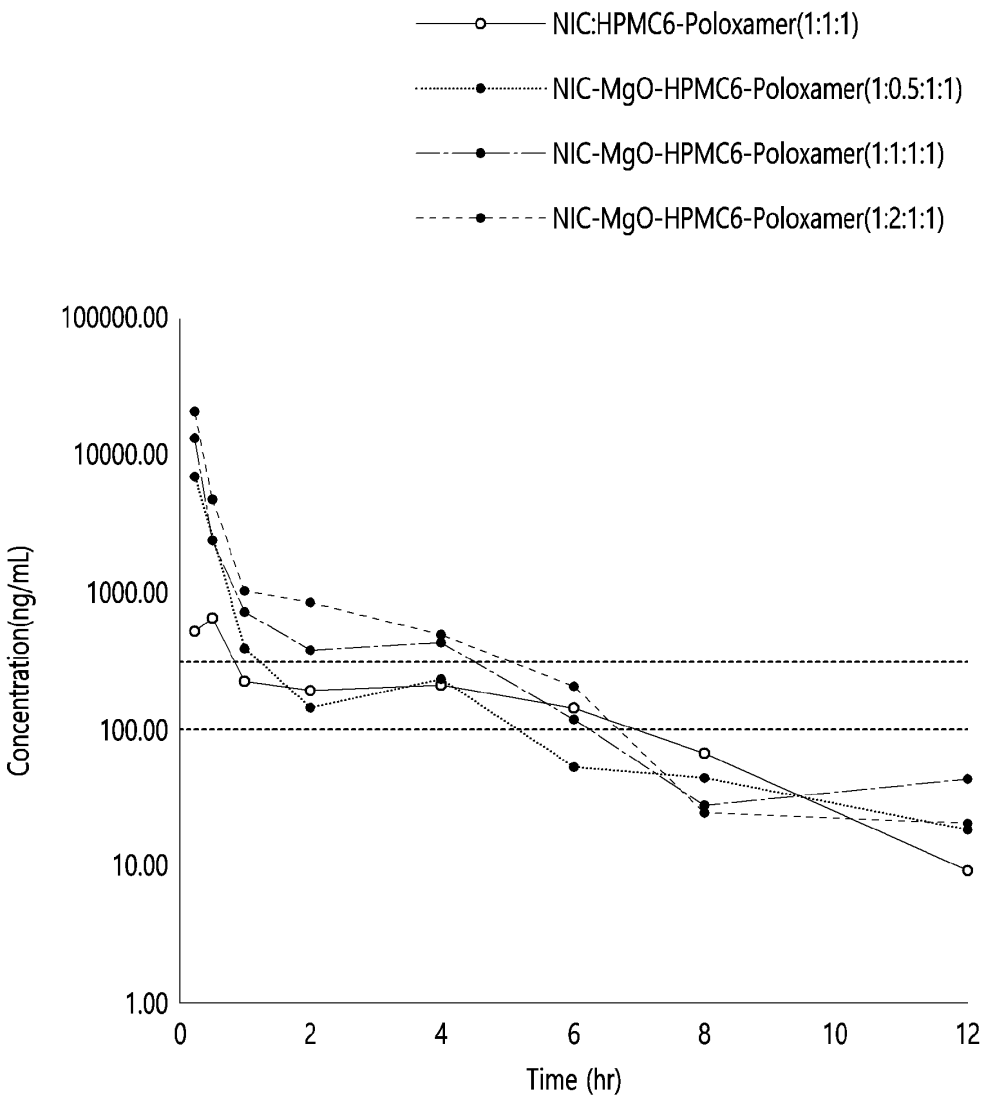
[도37]


70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
방출량(%)
0
20
40
60
80
100
120
시간(분)
Yomesan
D56H
HT
Mg(OH)2
MgO

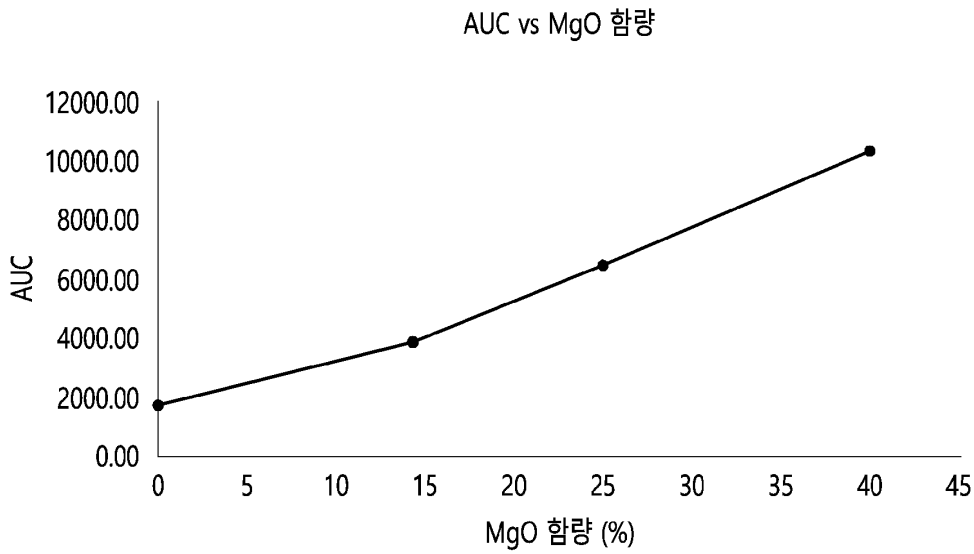
[도38]


40000
35000
30000
25000
20000
15000
10000
5000
0
Viral RNA copies/mL
P=0.048
감염대조군
Yomesan
실시예 11

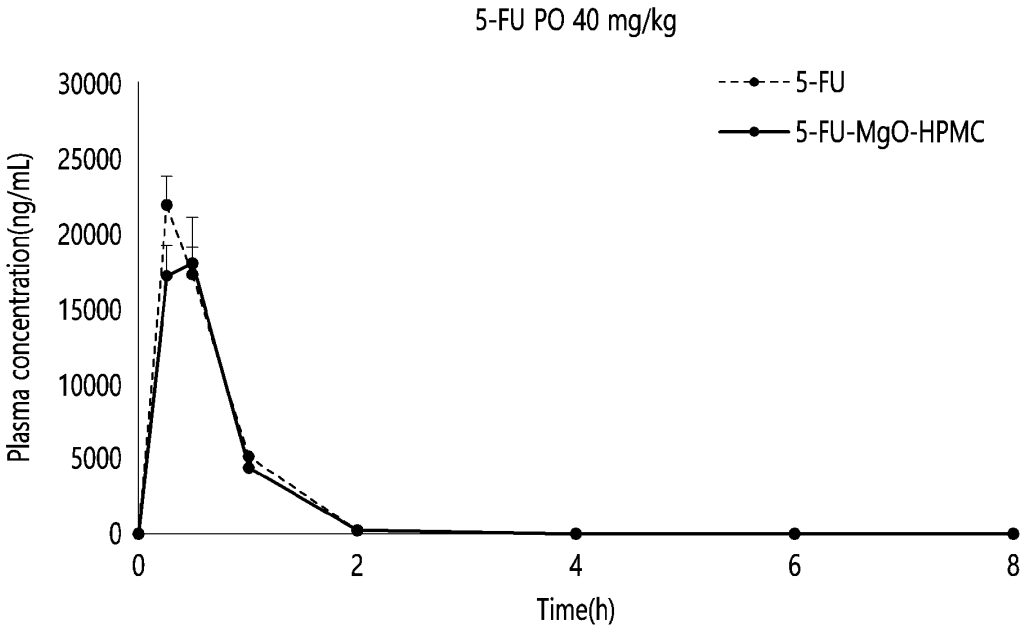
[도39]


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)

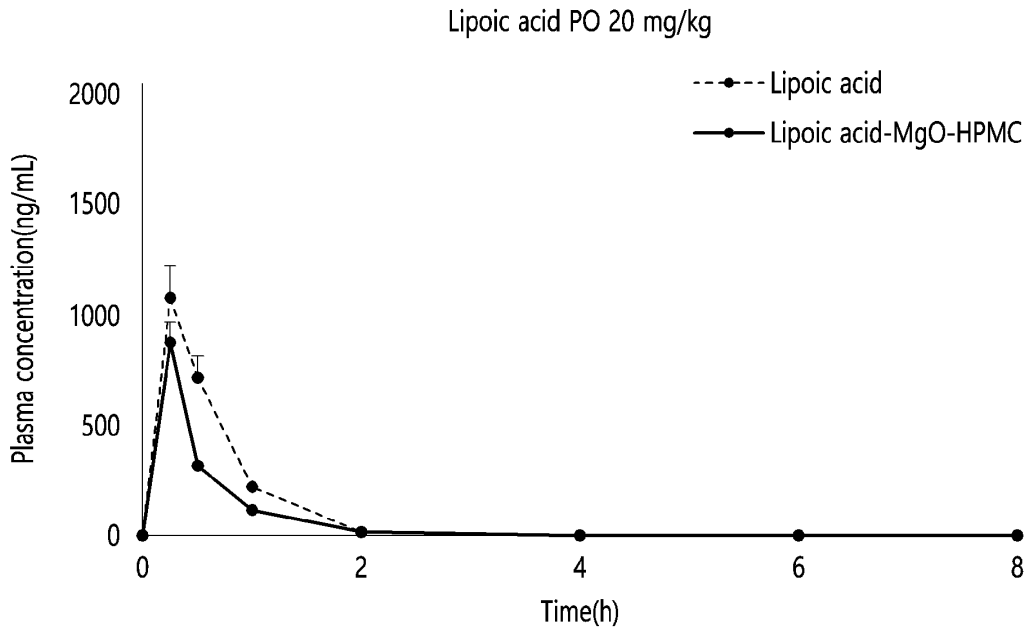
[도40]


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

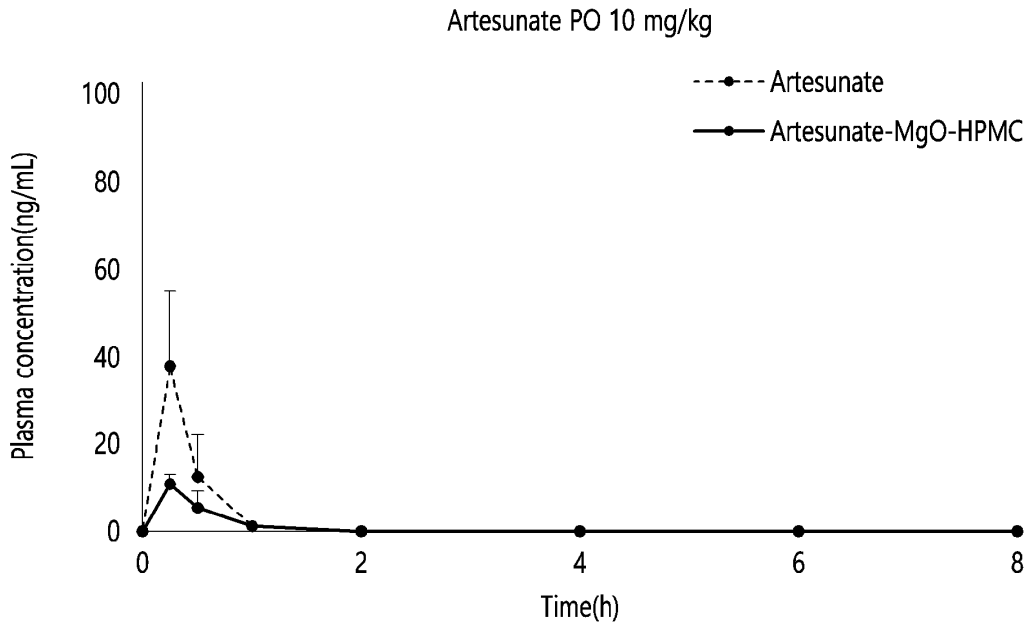
[도41]


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)

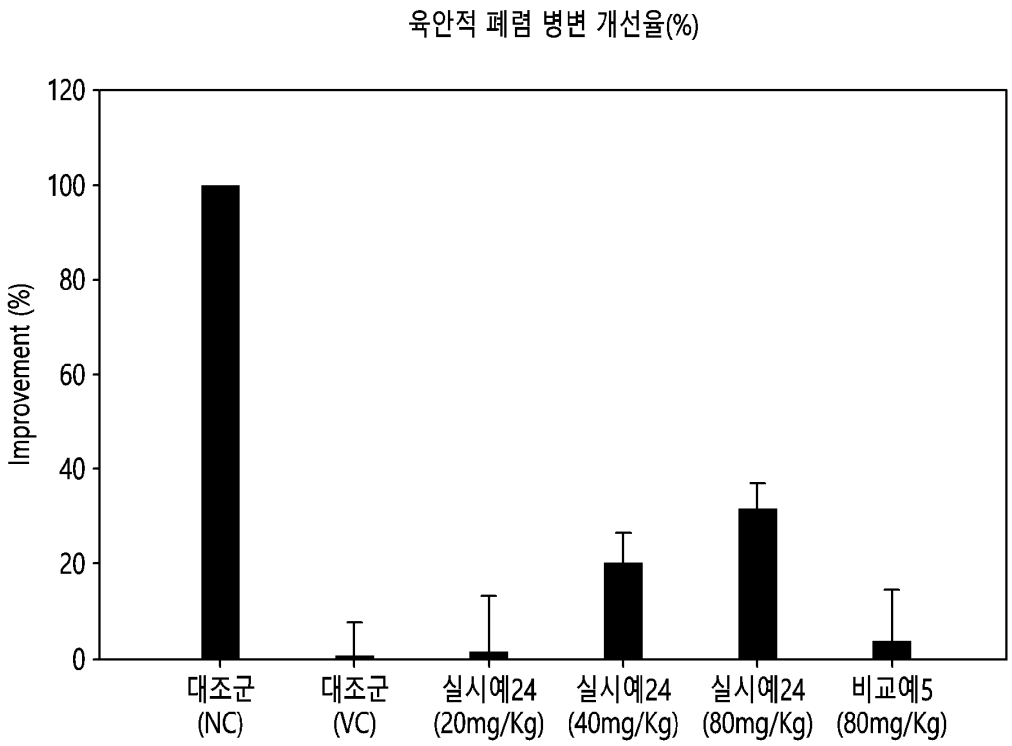
[도42]


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)

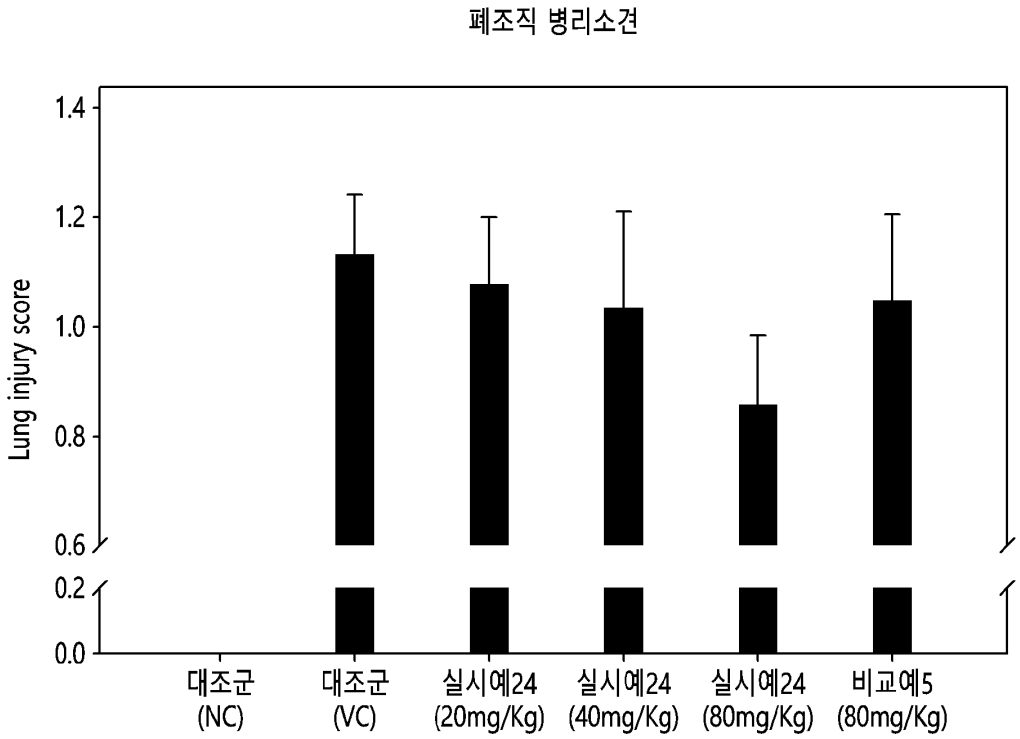
[도43]


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)

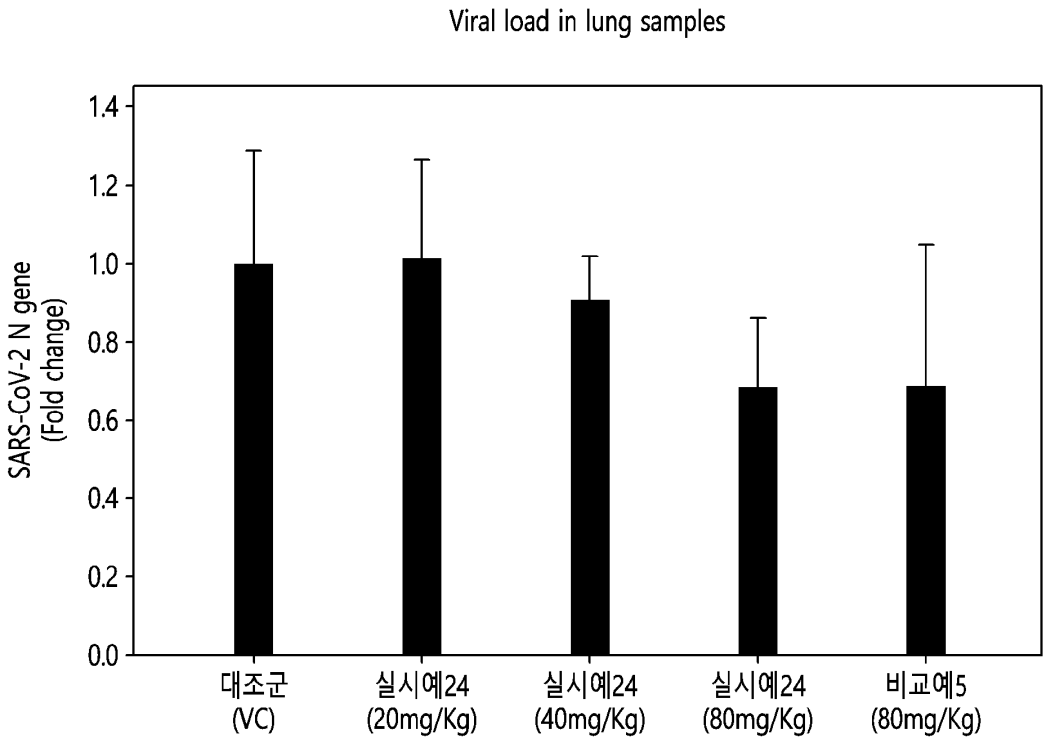
[도44]


육안적 폐렴 병변 개선율(%)
Improvement (%)
120
100
80
60
40
20
0
대조군 (NC)
대조군 (VC)
실시예24 (20mg/Kg)
실시예24 (40mg/Kg)
실시예24 (80mg/Kg)
비교예5 (80mg/Kg)

[도45]


폐조직 병리소견
Lung injury score
1.4
1.2
1.0
0.8
0.6
0.2
0.0
대조군 (NC)
대조군 (VC)
실시예24 (20mg/Kg)
실시예24 (40mg/Kg)
실시예24 (80mg/Kg)
비교예5 (80mg/Kg)

[도46]


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
대조군
(VC)
실시예24
(20mg/Kg)
실시예24
(40mg/Kg)
실시예24
(80mg/Kg)
비교예5
(80mg/Kg)

[도47]

