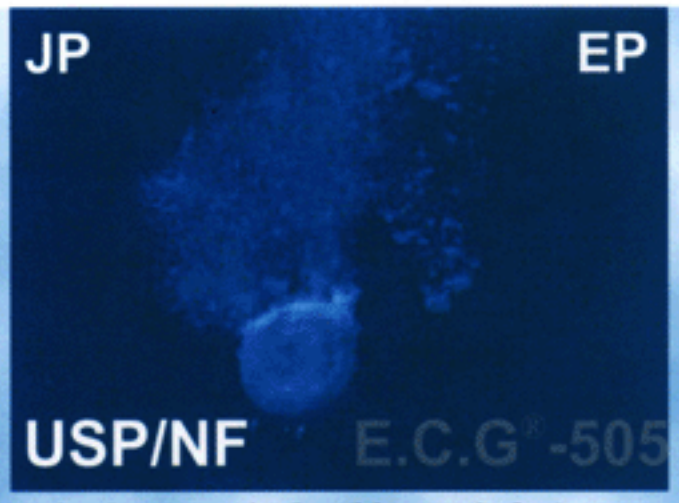


Carboxymethylcellose Calcium

CMC-Ca

Carmellose Calcium

[CAS 9050-04-8]

E.C.G®-505 NS-300®

Carboxymethylcellulose Calcium Carboxymethylcellulose

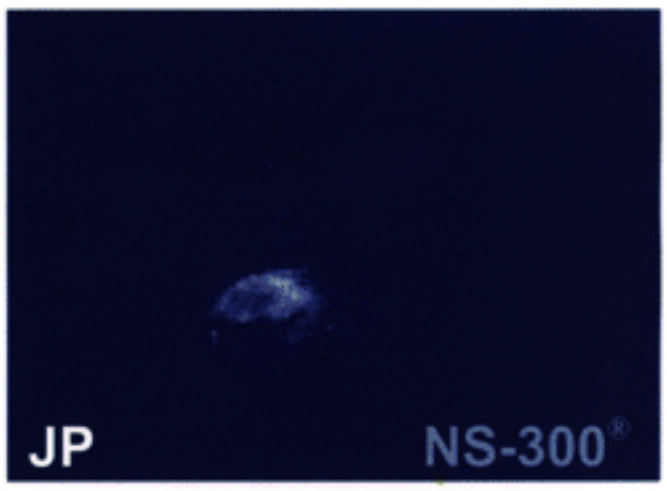
DISINTEGRANTS

Carboxymethylcellulose

CMC

Carmellose

[CAS 9000-11-7]



Sole Distributor

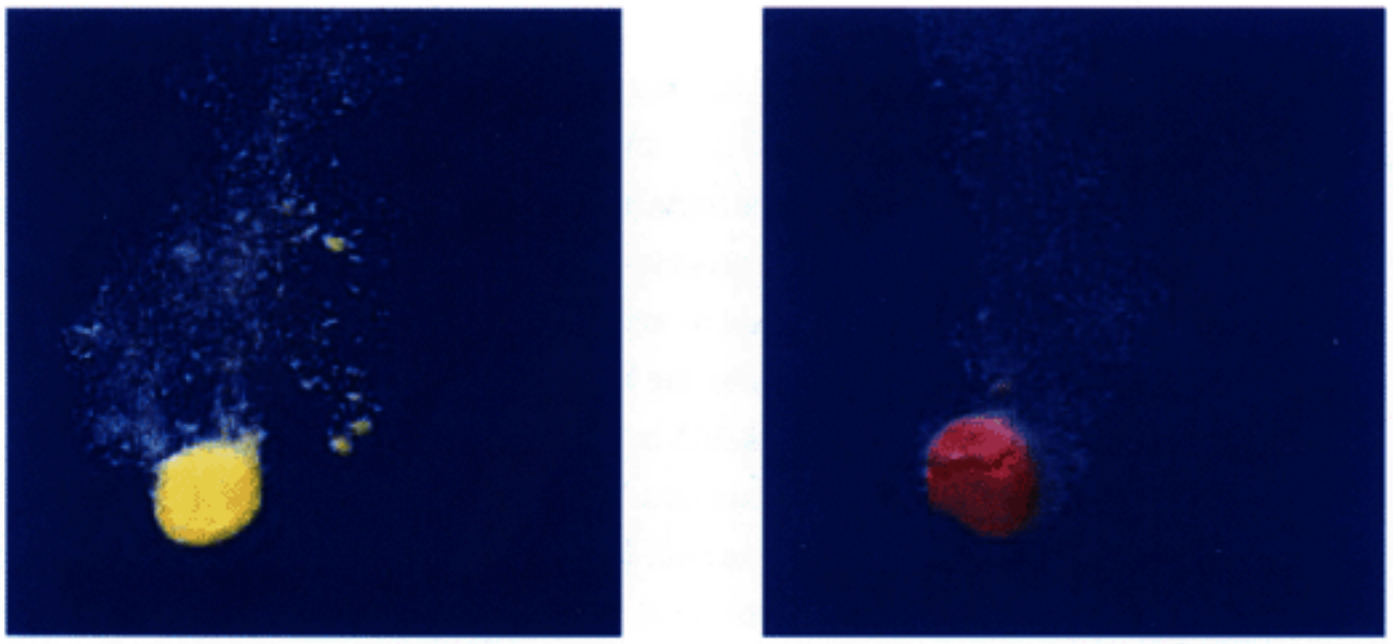
GOTOKU CHEMICAL COMPANY LTD.

Carboxymethylcellulose Calcium
CMC-Ca Carmellose Calcium
[CAS 9050-04-8]

Trade Name **E.C.G®-505**

Carboxymethylcellulose
CMC Carmellose
[CAS 9000-11-7]

Trade Name **NS-300®**



DISINTEGRANTS

INTRODUCTION

Two different types of carboxymethylcellulose were originally developed by GOTOKU CHEMICAL CO., LTD. One is a calcium type "ECG-505"and the other is a free type "NS-300'.

ECG-505 was manufactured in 1962 and its production patent was granted on March 26,1968. The manufacture of NS-300 began in 1967.

In Japan ECG-505 has received the highest favorable evaluation.

ECG-505 and NS-300 have been produced under strict quality control conditions by NICHIRIN CHEMICAL INDUSTRIES LTD which is a subcontract factory with the excellent plant.

ECG-505 and NS-300 have been widely used as agents for disintegration and dispersion of tablets and granules. This dispersion is one of the necessary state to attain the higher bioavailability of drug.

ECG-505 was published in JP in 1966.

ECG-505 was published in USP-XXI, US-NF X VI in 1985 and in EP in 1994.

NS-300 was also published in JP in 1986.

In 1992, ECG-505 was chosen among the 25 most frequently used pharmaceutical excipients in International Harmonization Monographs and NS-300 was also chosen as an addendum item to those of ECG-505.

I. Characteristics of ECG®-505 and NS-300®

ECG-505 and NS-300 are made up of cellulose modified by carboxymethylation.
ECG-505 is the only disintegrant, among many disintegrants in the world, containing calcium as a component.
NS-300 is produced by lowering carboxymethylcellulose sodium's pH by an acid treatment.
ECG-505 and NS-300 rapidly absorb the water needed for swelling and consequently show a very short disintegration time.
The process of dispersion to granule and powder caused by the disintegration of tablets and granules is very important for promoting the solubility and thereby the bioavailability of drugs.
ECG-505 is insoluble but shows hydrophilic property in water due to its chelate structure and calcium component. NS-300 of carboxylic acid type shows poor hydration but shows a sufficient disintegration function by its electrostatic repulsive force.
Although in practice, ECG-505 has been favorably used more than NS-300 in pharmaceutical formations, one drawback is that the calcium component interact with some medicines which contain phosphate or sulfate. In these cases, NS-300 is used instead of ECG-505.

Advantages of ECG-505 and NS-300

1. Rapid Disintegration.

ECG-505 and NS-300 are superior to starch in their disintegration abilities. ECG-505 has a higher ability of absorbing the water necessary to cause swelling due to its chelate structure and calcium component.

2. Release and Dissolution.

A higher drug release and dissolution property is very important for promoting bioavailability of tablets and granules. ECG-505 and NS-300 rapidly disintegrate tablets and granules, although they are insoluble in water.

3. Compressibility.

Because of their fibrous shape, ECG-505 and NS-300 have a high compressibility as well as a high disintegration property.
The tablets and granules formulated with ECG-505 and NS-300 show both a very short disintegration time and high mechanical strength based on their high compressibility.

4. Stability.

ECG-505 and NS-300 show a high long-term stability in various tablet and granule prescriptions. However, ECG-505 may interact with some substances having phosphate and sulfate owing to its calcium.

II. The Chemistry of ECG®-505 and NS-300®.

ECG-505 is composed of the calcium salts of carboxymethylcellulose and NS-300 is the free form of carboxymethylcellulose which is a cellulose derivative formed by etherification with monochloroacetic acid under the alkali catalyst.

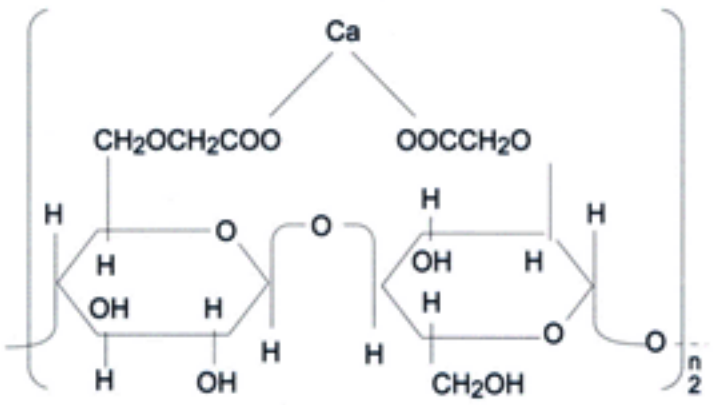
Both products are a white, odorless, harmless and fine powder.

Both are practically insoluble in ethanol and ether. They absorb water and swell with water to form suspension.

The chemical structure formula of ECG-505 is shown in Fig-l-A and that of NS-300 is shown in Fig-l-B.

Fig-1-A

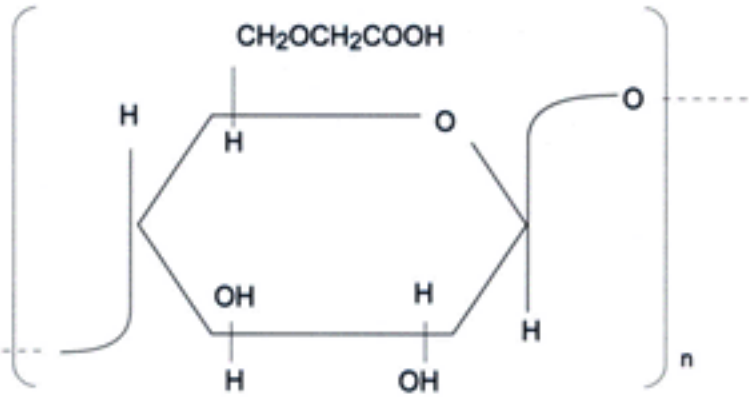
ECG-505



Molecular formula:
$[C_6H_7O_2(OH)_{3-x}(OCH_2COO)_x1/2Ca_x]_n$

Fig-1-B

NS-300



Molecular formula:
$[C_6H_7O_2(OH)_{3-x}(OCH_2COOH)_x]_n$

x:Degree of substitution
n:Degree of polymerization

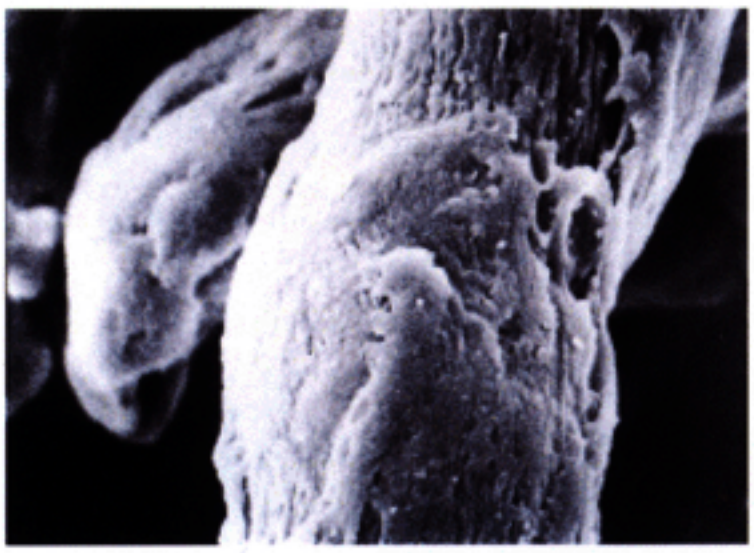
Properties of ECG®-505 and NS-300®

	ECG-505	NS-300
Degree of substitution	0.5-0.7/C_6	0.4-0.6/C_6
Particle through 200mesh	more than 95%	more than 95%
Bulk Density	500-600g/L	300-400g/L
Solubility: Distilled water 0.1N NaOH	insoluble swellable gelation	insoluble swellable gelation
PH	4.5-6.0	3.5-5.0
Stability: sunlight	stable	stable
Humidity:	see Fig-2	see Fig-3

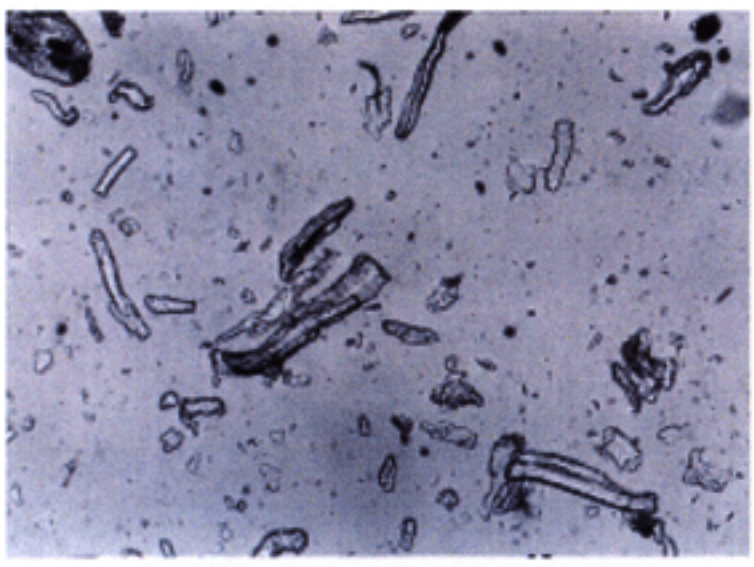
Microscopic photograph of ECG®-505 and NS-300® are shown in Fig-l-C.

Fig-1-C

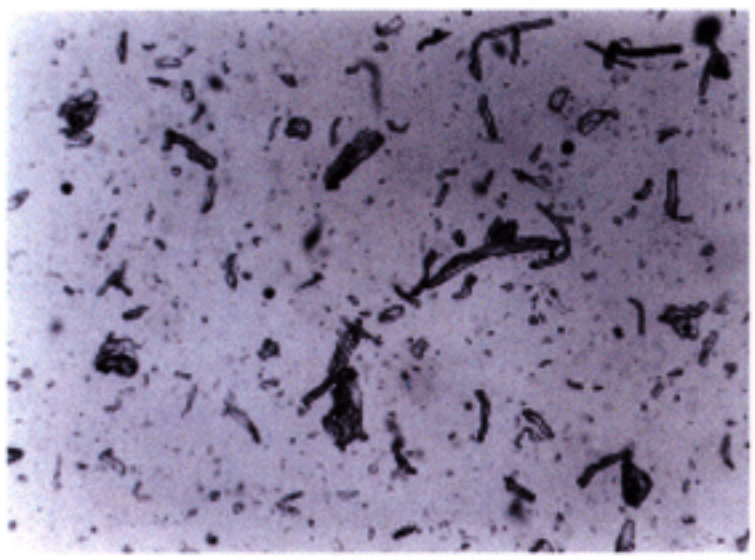
Microscopic photograph of E.C.G® -505



Electron- Microscopic photograph(X3000)

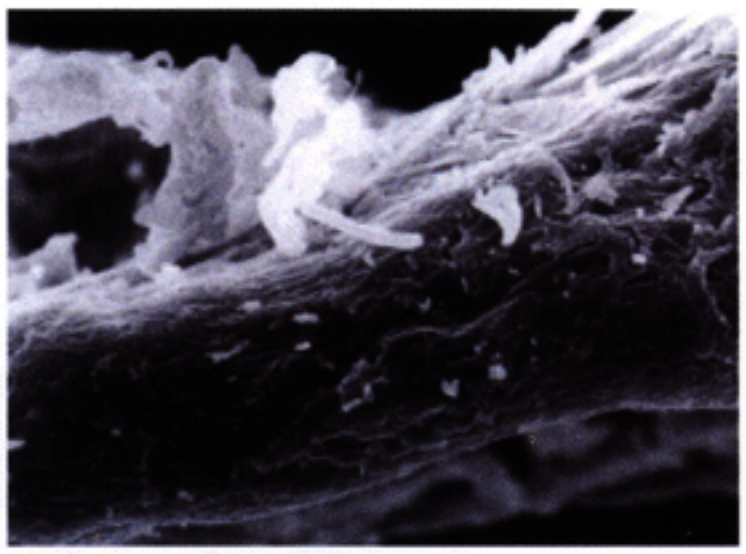


Optical- Microscopic photograph(X50)

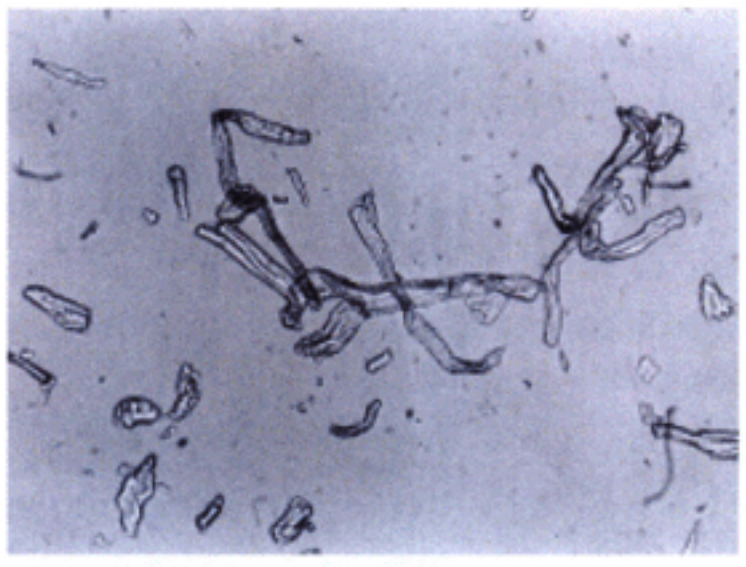


Optical- Microscopic photograph(X20)

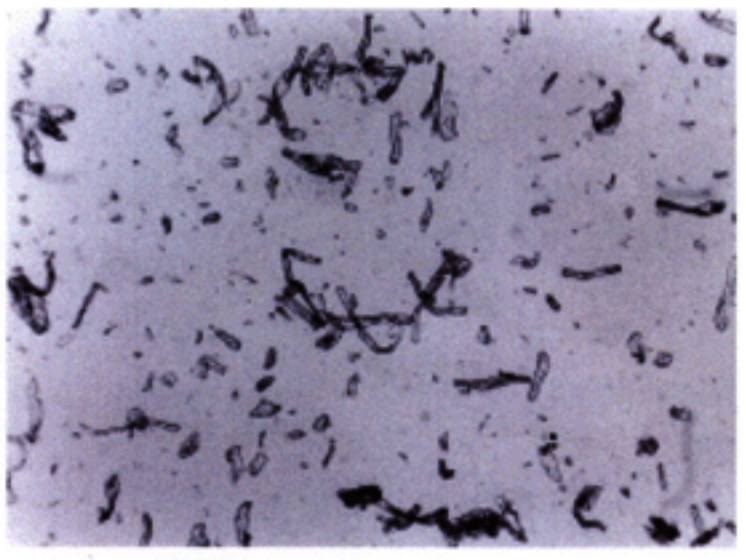
Microscopic photograph of NS-300®



Electron- Microscopic photograph(X3000)



Optical-microscopic photograph(X50)



Optical-microscopic photograph(X20)

III. Equilibrium Moisture Content and Moisture Absorption of ECG®-505 and NS-300®

Fig-2:Relative humidity and equilibrium moisture content(at 25°C)

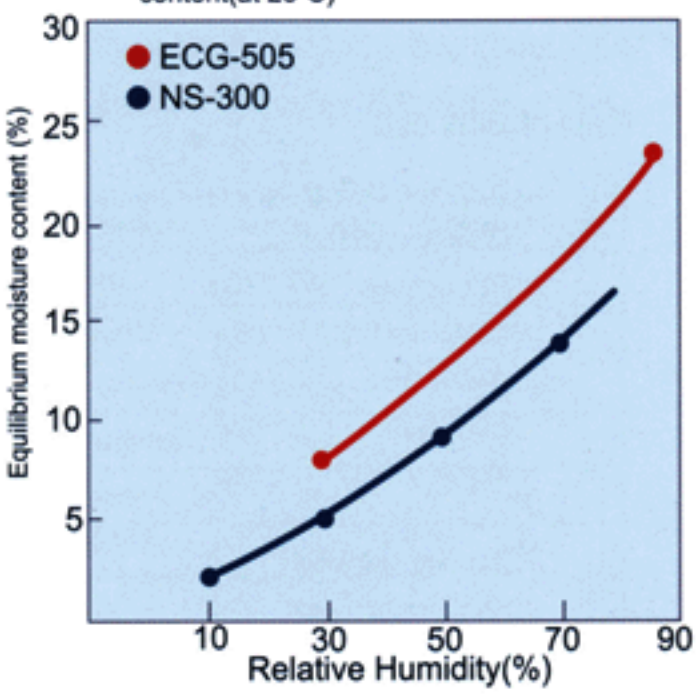
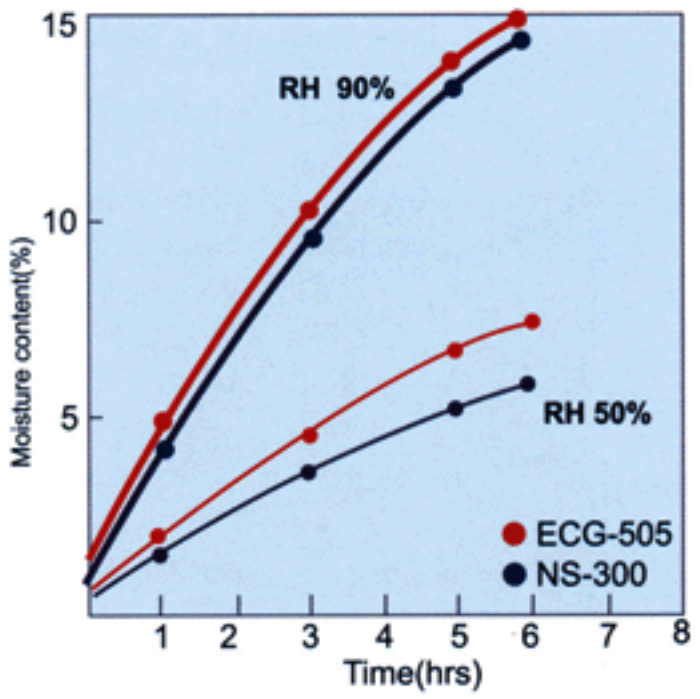


Fig-3:Absorption rate of moisture content



IV. The general tableting test

Relationship between loss on drying of disintegrants and hardness.

Composition :

A: 100% of disintegrant

B: 20% of disintegrant +80% of aspirin

C: 20% of disintegrant +80% of lactose

Three kinds of tablets containing ECG-505 and NS-300 were directly compressed with various amounts of loss on drying.

The relationship between hardness of tablets and loss on drying is shown in Fig-4:A, 5:B, 6:C. Resultant hardness increases with increase of loss on drying of tablets.

Fig-4:A composition

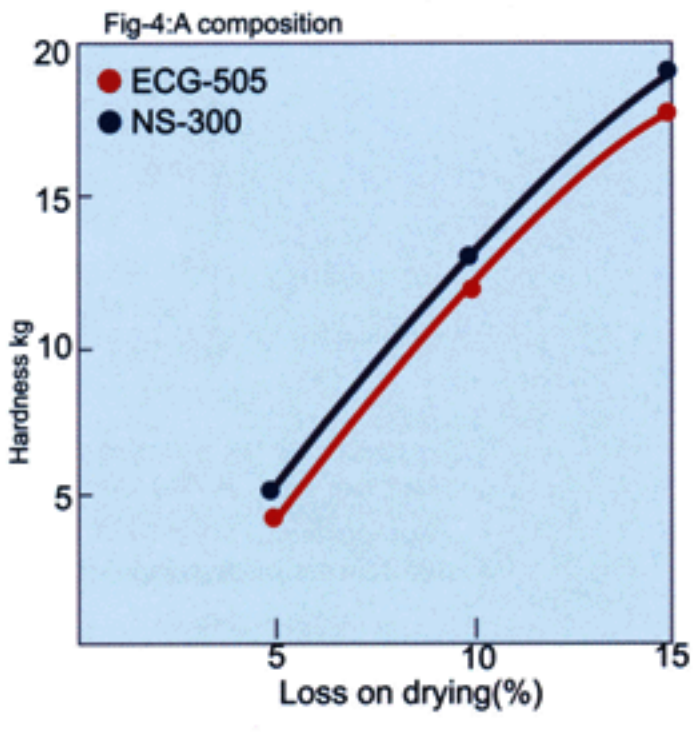


Fig-5:B composition

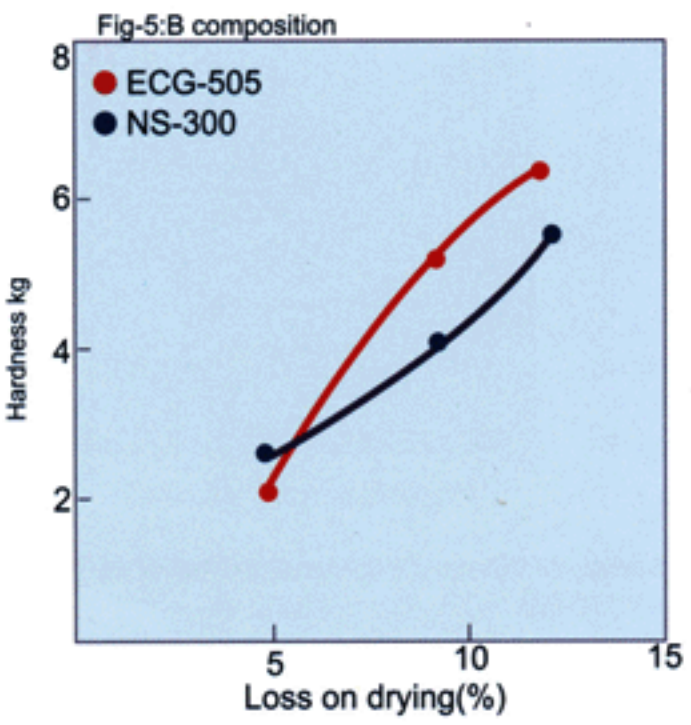
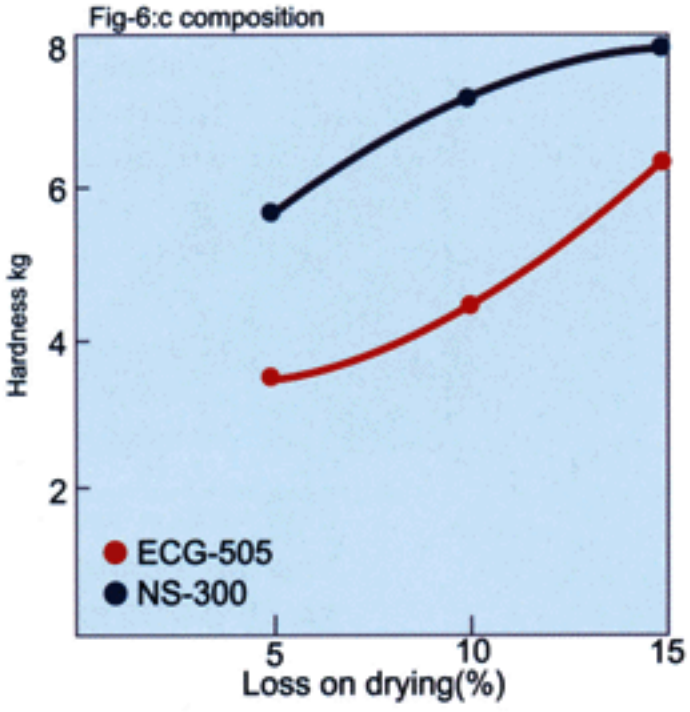


Fig-6:c composition



V. Compression test of ECG®-505 and NS-300®.

Several tablets were prepared by two methods such as Wet Granulation and Direct Compression and then were measured the hardness and disintegration time as shown in Table-1 and Table-2.

Case of ECG-505

	A:Wet Granulation		B:Direct Compression	
Method:				
Composition:	Dibasic calcium Phosphate	970g	Dibasic calcium Phosphate	770g
	ECG-505	30g	Lactose#100	55g
	Mg-St	3g	Avicel 101	145g
			ECG-505	30g
			Mg-St	3g
Process:	Dibasic calcium Phosphate ECG-505		Dibasic calcium Phosphate Lactose#100 Avicel 101 ECG-505	
	↓ mixing		↓ Mixing	
	↓ add 10g of 8% MC paste		↓ add Mg-St	
	↓ kneading		↓ Mixing	
	↓ 20mesh sieving		↓ tableting	
	↓ wet granules			
	↓ drying			
	↓ dried granules			
	↓ add Mg-St			
	↓ tableting			

Mg-St:Magnesium stearate

Results of measurement

Table-1

	A	B
average weight	199.8 mg	200.0 mg
average hardness	5.1 kg	9.0 kg
Disinteg-ration time	1min>	1min>

Case of NS-300

	A:Wet Granulation		B:Direct Compression	
Method:				
Composition:	Lactose G	100 parts	Lactose G	100 parts
	NS-300	1,3,5,7,10%	NS-300	0.5,1,2,5,10%
	Mg-St	0.5%	Mg-St	0.1%
Process:	Lactose G NS-300 each%		Lactose G NS-300 each%	
	↓ mixing		↓ mixing	
	↓ add ethyl alcohol		↓ add Mg-St	
	↓ kneading		↓ mixing	
	↓ 200mesh sieving		↓ tableting	
	↓ wet granules			
	↓ drying			
	↓ dried granules			
	↓ add Mg-St			
	↓ tableting			

Measurement:
Disintegration time:min

Table-2

Amounts of NS-300(%)	A	B
0	17.1	17.0
0.5		11.4
1.0	15.7	5.6
2.0		1.9
3.0	3.7	
5.0	4.0	0.8
7.0	2.8	
10.0	4.0	0.8

Disintegration time:
Time was measured in the water by the Auto-disintegration Tester of TOYAMA SANGYO NT-2 type)
Additional amounts of NS-300 as disintegrant is desirable to be more than 3% because of its property of slightly poor hydration.

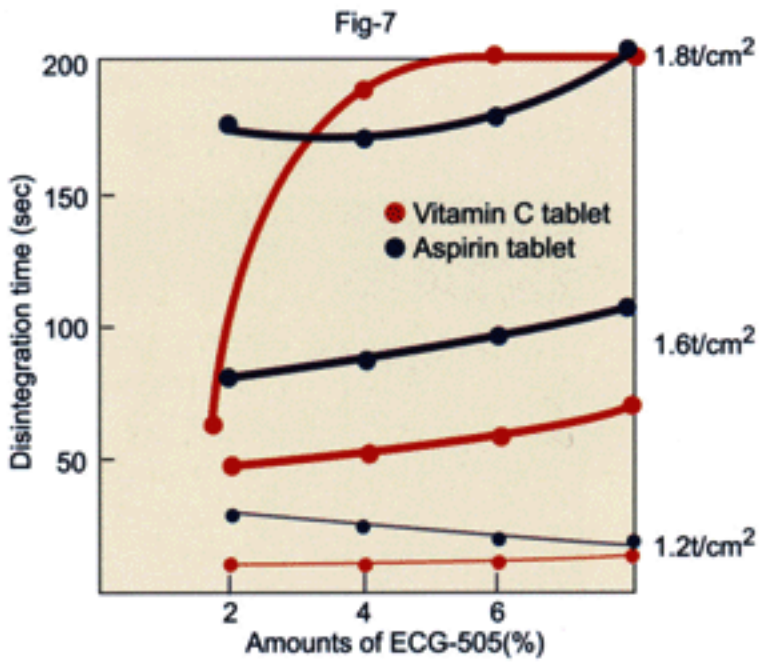
VI. Application of ECG®-505 and NS-300®

EX-l: Application of ECG-505

ECG-505 was formulated as a disintegrant in Aspirin tablet and Vitamin C tablet and the disintegration time of these tablets were measured.

Composition:	Aspirin tablet	VitaminC tablet
Aspirin:	55g	-----
Vitamin C:	-----	50g
Avicel PH-101:	27-xg	47-xg
Lactose#100	15g	-----
ECG-505:	xg	xg
Mg-St:	-----	0.5g
Lubri:	0.5g	-----
Talc:	2g	2.5g

Fig-7



Tablets containing ECG-505 were compressed with the direct compression force 1.8t/cm², 1.6t/cm² and 1.2t/cm² by using a rotary tableting machine. The results are shown in Fig-7.

EX-2: Application of NS-300

NS-300 is produced by lowering carboxymethylcellulose sodium's pH by an acid treatment. NS-300 stabilizes drug in a higher pH condition by its acidity and acts as a lubricant to tablet by its replusive force and fibrous. Tableting troubles, capping and sticking etc, will be prevented by this reasons. Therefore NS-300 is used widely in pharmaceutical formation. Furthermore the addition of NS-300 to commercially available tablet containing aspirin is effective on the disintegration time and the release rate of aspirin tablets as shown in Fig-8-1 and Fig-8-2.

Fig-8-1

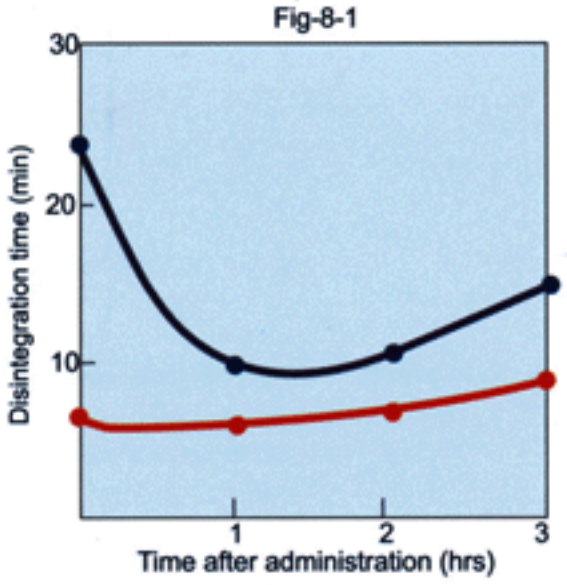
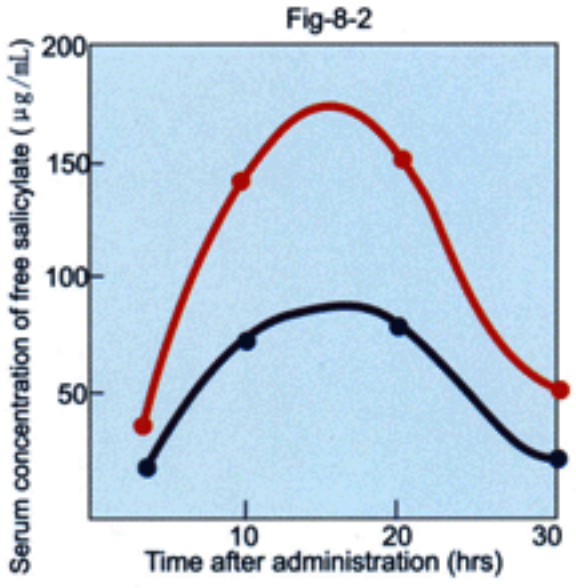


Fig-8-2



● commercially available tablet containing aspirin
● addition of 3.4%of NS-300 to tablet containing aspirin

VII. Examples of a good disintegration by ECG®-505 and NS-300®

EX-1: Improvement of hardness and disintegration time of a crude drug.
Senna Leaf powder 750mg, synthetic aluminum silicate 100mg, dibasic calcium phosphate 200mg were mixed with various disintegrants 225mg and the mixtures were compressed by Direct Compression and the hardness and disintegration time were measured. The results were divided into the following two groups as shown in Table-3.

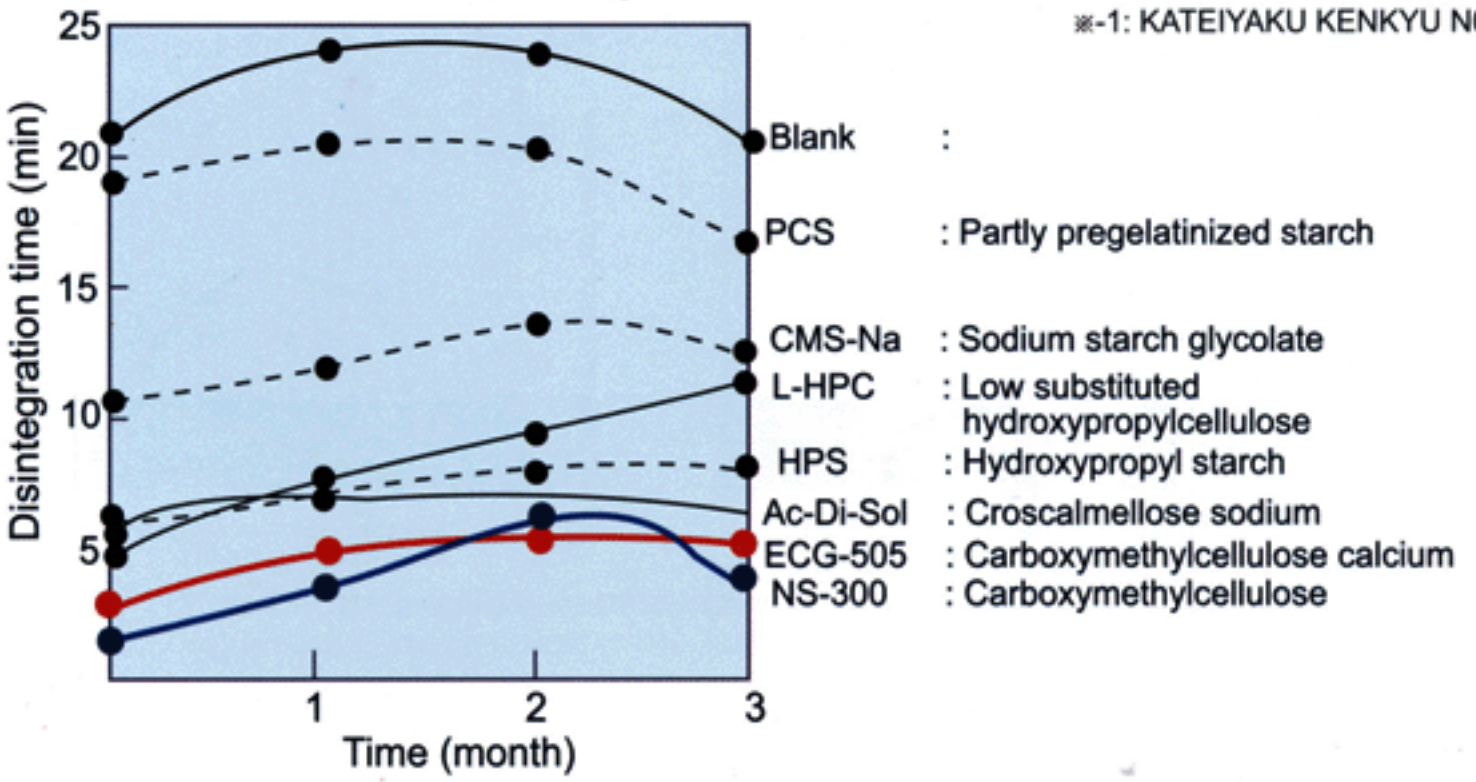
Table-3

	Cellulose group		starch group		
Disintegrant	Disintegration time (min)	hardness kg	Disintegrant	Disintegration time (min)	hardness kg
NS-300	3	13.2	Explotab	5	5.0
ECG-505	8	7.0	PCS	16	4.3
L-HPC	17	20.0	Starch	30<	5.6

Disintegrants of cellulose group showed higher hardness and shorter disintegration time than those of starch.
NS-300 and ECG-505 in particular are found to be excellent disintegrants in this examination.

EX-2: Comparative study on a variety of commercially available disintegrants.
Toyama Pharmaceutical Research Association examined the effects of several disintegrants by tablets formulated with lactose 95%, L-HPC 2%, St-Mg 0.5% and each disintegrant 2%. Blank was not added any disintegrants. ※-1
In this report, the relationship between disintegration time and storage time is exhibited as shown in Fig-9.
Cellulose groups(straight line)are superior to starch groups(dotted line) in disintegration time.

Fig-9



※-1: KATEIYAKU KENKYU N0.12. 41. (1993)

XIII. Disintegration time and dissolution of drug in tablets containing several disintegrants.

1. The relationship between amounts of disintegrants and disintegration time of tablets containing 70% of acetoaminophen is shown in Fig-10.
   Each tablet is combined with one of 4 kinds of disintegrants such as ECG-505, NS-300, L-HPC and Ac-Di-Sol.

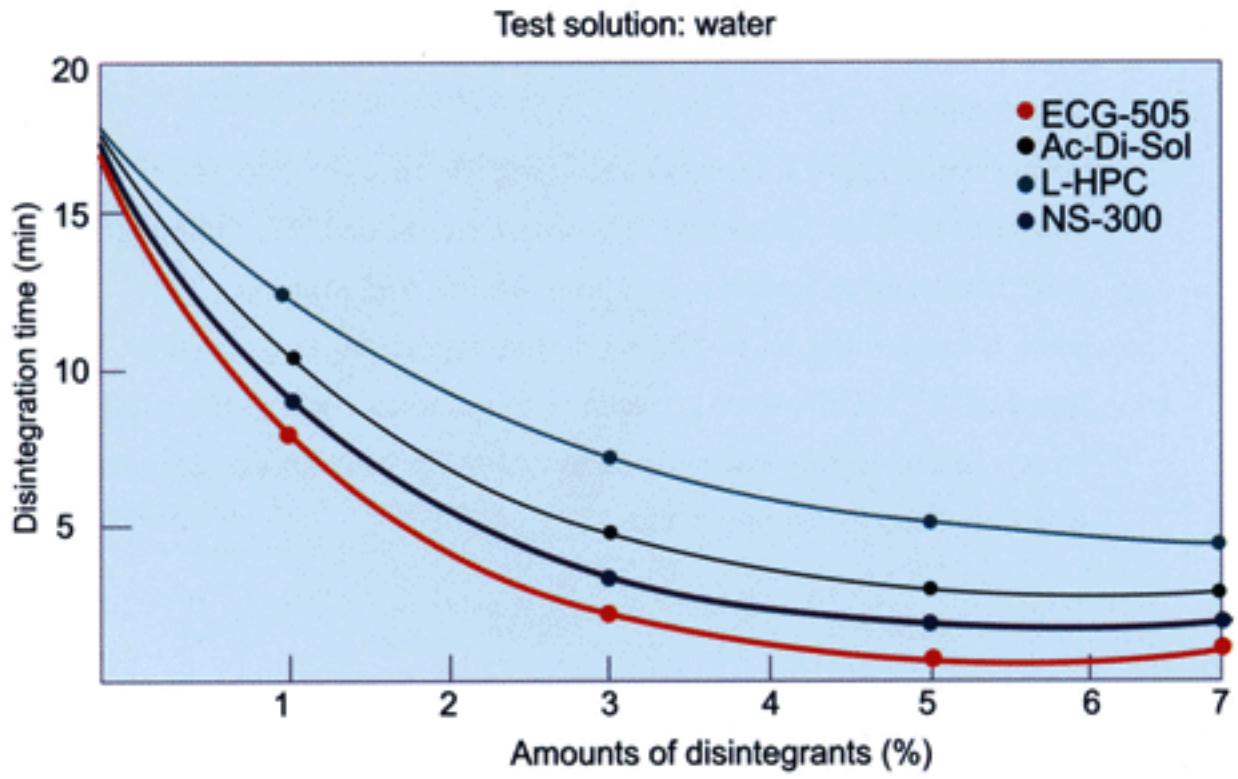


Fig-10: Disintegration time of 4 kinds of tablets containing 70% of acetaminophen.

2. The relationship between amount of dissolution and time of tablets containing 70% of ethenzamide is shown in Fig-11.
   Each tablet is combined with one of 4 kinds of same disintegrants mentioned above and control tablet is not added any disintegrants. Fig-11 shows that dissolution (%) made no great difference between 4 kinds of disintegrants except for control.

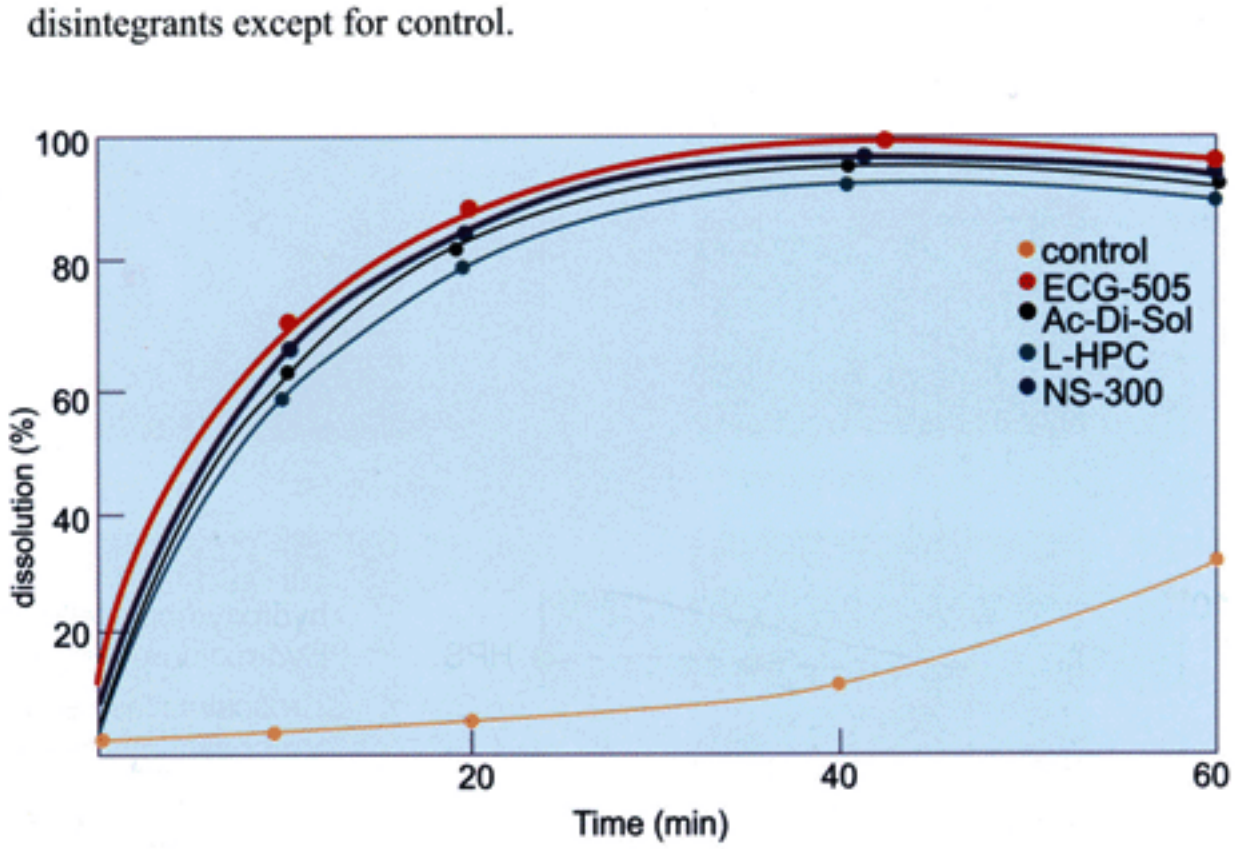


Fig-11: dissolution(%) of 5 kinds of tablets containing 70% of ethenzamide

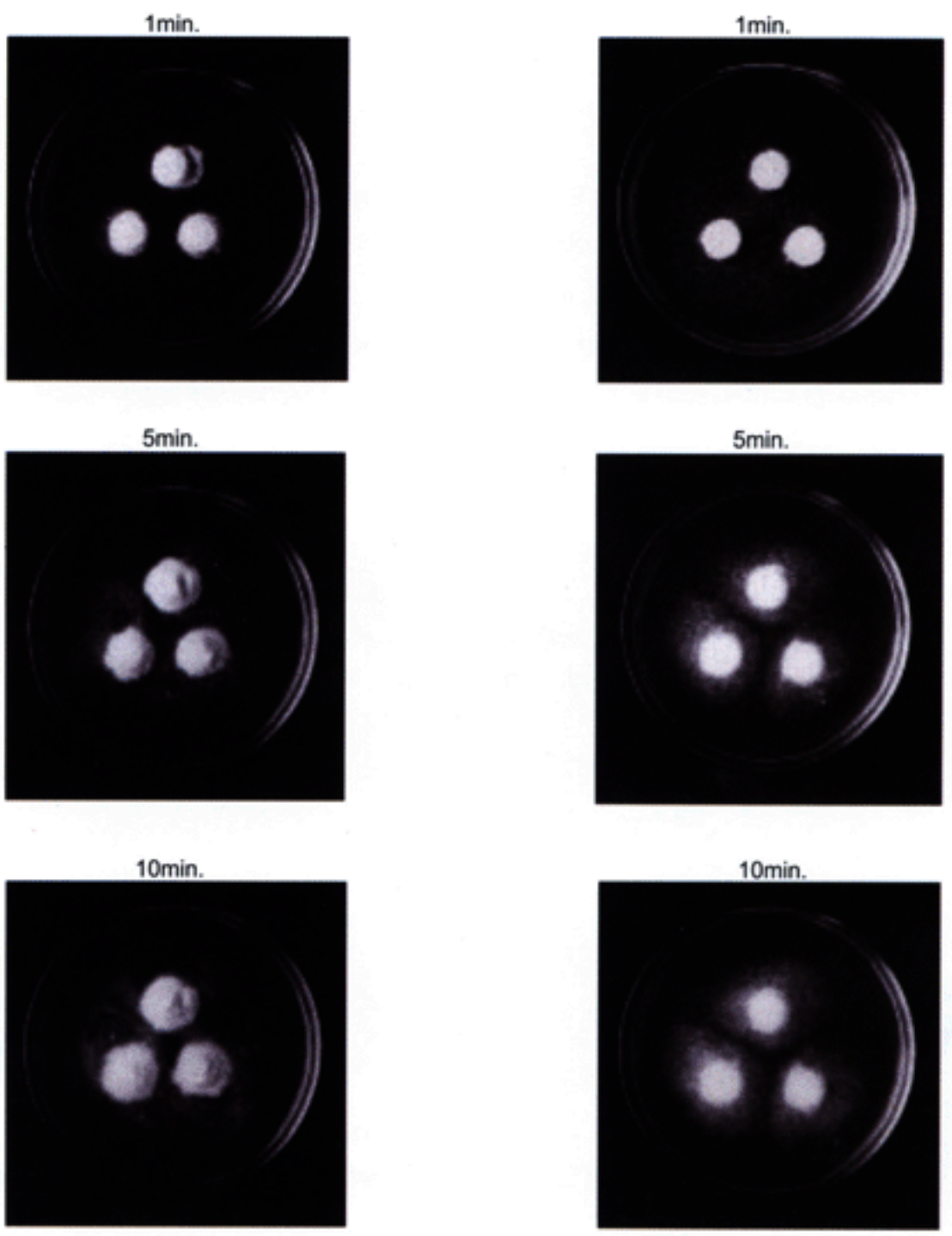
IX. Comparative test of disintegration by using tablets containing ECG®-505 and NYMCEL

Tablets for the disintegration test were prepared with Lactose-G containing ECG-505 and NYMCEL by Direct Compression method.
The hardness of tablets were in the range between 5.0 and 6.0kg.

NYMCEL: low substituted sodium carboxymethylcellulose.

Test method:
As shown in Fig-12, tablets containing 5% of ECG-505 and 5% of NYMCEL were put in Petri dishes and then water was added. The disintegrative states were observed at intervals of 1 min, 5mins, and l0mins.
Tablets containing ECG-505 were disintegralated very quickly. In contrast, those of NYMCEL were covered with gelatinous gel at the surface of tablets, which inhibited internal permeation of water into tablets and resulted in poor disintegration as shown in Fig-12.

Fig-12

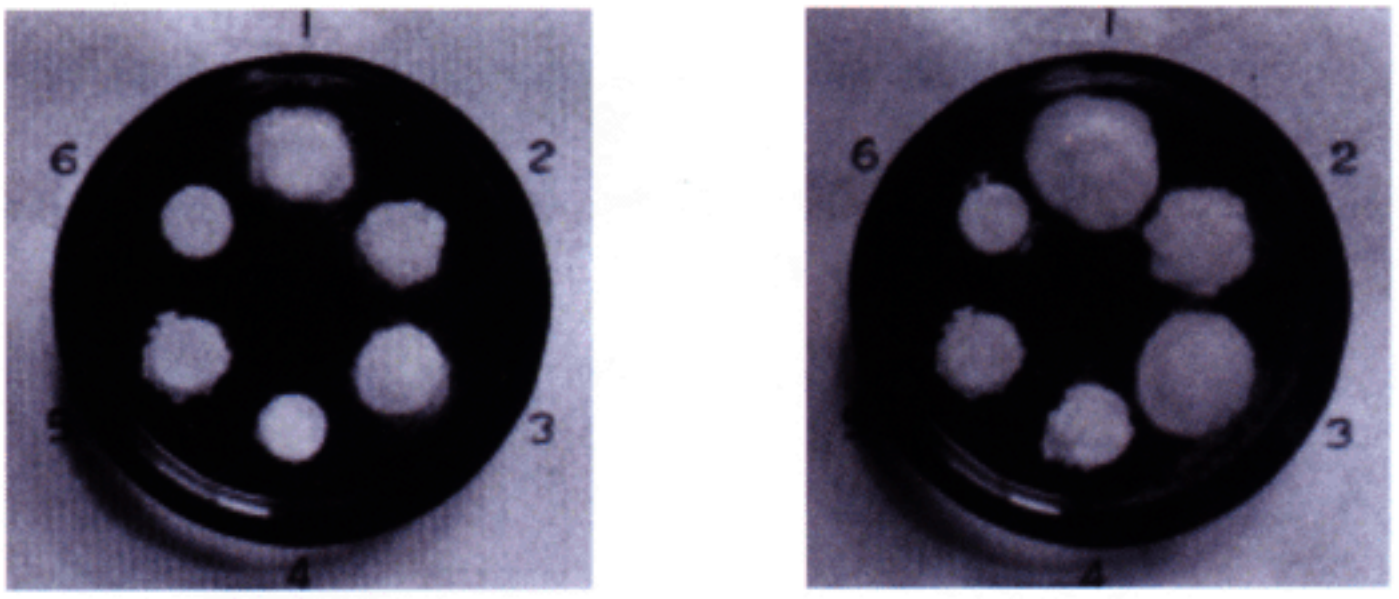


x. Comparative test of disintegration time by using tablets containing several disintegrants.

The tablets containing six kinds of disintegrants were prepared using the same conditions as the abovementioned method.

These six tablets were put in one Petri dish all together.
The same test method was used as the abovementioned method, except that the No.l solution of JP was used instead of water.
As shown in Fig-13, the tablet containing ECG-505 was observed as the best disintegrant in this test.

Fig-13



30seconds　　1minute

1. ECG-505:　carboxymethylcellulose calcium
2. Primojel:　sodium carboxymethyl starch
3. Polyplasdone XL:　Cross-linked polyvinylpyrrolidon
4. L-HPC:　low substituted hydroxypropylcellulose
5. Ac-Di-Sol:　croscalmellose sodium
6. Avicel:　microcrystalline cellulose

E.C.G® -505 NS-300®

PACKING: ECG-505: (1) Fiber drum with a polyethylene inner bag containing net weight 50kg.
(2) 20kg Carton box with polyethylene inner bag containing net weight 20kg.

NS-300: (1) Fiber drum with a polyethylene inner bag containing net weight 50kg.
(2) 20kg Carton box with polyethylene inner bag containing net weight 20kg.

STORAGE: Store in a cool and dry place.
Store away from heat and sunlight.

WARNING: When handling in large quantities, take precautions to avoid accumulation of dust in the air.
If contact is made with eyes, rinse with water for 10 mins.

POSTSCRIPT: For more information, please contact GOTOKU CHEMICAL CO., LTD. directly.
Any inquiries about ECG-505 and NS-300 can be directed to GOTOKU CHEMICAL CO., LTD.
(GOTOKU CHEMICAL----------Sole Distributor)

E.C.G®-505 and NS-300® were originally developed by
GOTOKU CHEMICAL CO.,LTD.
GOTOKU CHEMICAL is controlling the whole market,
domestic and overseas, as the sole distributor of
E.C.G®-505 and NS-300®
For more information, please contact GOTOKU CHEMICAL directly.

Sole Distributor

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