

Pharmacoat Coating in an Aqueous System : The Dissolution Behavior and Reduction in Coating Time

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Summary

It is sometimes said lately that the pH of the human gastric juice is significantly different among individuals. Thus, the dissolution behavior of coated solid dosage forms should preferably be independent of the pH of the test solution. With these points as a background, the effect of pH on the dissolution velocity of coated tablets was studied to compare that of Pharmacoat with other gastric soluble film coating materials.

Three viscosity types of Pharmacoat have been available(3, 6 and 15cP) until now. The 6cP type has been considered to be the most suitable for a tablet coating amongst the three types.

The 3 cP type with a low degree of polymerization, is capable of providing high concentration, but the film strength is so inferior that sometimes cracking of the film may occur.

On the other hand, in the case of the 15cP type, high polymer concentration cannot be achieved because of the high degree of polymerization, and thus it is uneconomical for coating. Now, there is a strong demand to reduce the coating time even when HPMC is used in the 6cP type in order to reduce the coating cost. In order to improve this problem, we have concentrated our attention on reducing the viscosity value of HPMC to an allowable lower limit from 6cP. As a result of this study, it was found that the reduction of the viscosity value to around 4.5cP enabled the use of a higher solution concentration and an incidental shorter coating time without giving any substantial adverse effects on the properties of coated preparations. These experiment results are presented in the later part of this presentation.

Based on this study, we have added the viscosity type of 4.5cP as one of the Pharmacoat products as Pharmacoat-645.

Contents of the Presentation

(Table 1)

An outline of hydroxypropyl methylcellulose is described. Low viscosity types of the material are most popularly used as a gastric soluble coating material and a binder for solid dosage forms, while high viscosity types of it are sometimes used as a matrix base for a sustained release tablet.

(Table 2)

An outline of hydroxypropylcellulose is described. This material is popularly used as a binder for solid dosage forms. However, it is unusual to apply this material independently as a film coating material because of its stickiness.

(Table 3)

An outline of polyvinylacetal diethylaminoacetate is described. This material is soluble up to pH5.8 and thus it is expected to be easily soluble in gastric juice having such a pH range.

(Table 4)

An outline of aminoalkyl methacrylate copolymer E is described. This material is soluble up to pH5.0 and thus it is expected to be easily soluble in gastric juice having such a pH range.

(Table 5)

Vitamine B₂ (VB₂) was selected as the index drug material for studying the effect of pH on the dissolution profile of tablets coated with each coating material respectively. Tablets containing 2% of VB₂ were prepared by the wet granulation method using the formulation shown in this table.

(Table 6)

The properties of the obtained tablets are shown. It took approximately 15 minutes for complete dissolution of VB₂ in both the JP 1st fluid and in water.

(Table 7)

The formulation of the coating solution for each coating material is shown. The concentration of the coating material was set at a uniform 6%. In the cases of HPMC and HPC, aqueous systems were applied, while in those of vinyl polymer and acrylic polymer, organic systems were applied.

(Table 8)

The coating conditions are summarized in this table. As a coating apparatus, a small-sized side-vented pan was used. The quantity of the coating material applied was set at a uniform 4%.

(Table 9)

The conditions of the dissolution test are summarized in this table. Four tablets were tested in the dissolution test of the paddle method of the JP using the Clark-Lubs buffer solution at each pH value, the JP 1st fluid and water as the test solution respectively.

(Fig. 1)

The dissolution test results using water as the test solution are shown in the first chart of the figure. In the cases of vinyl polymer and acrylic polymer, no dissolution after 60 minutes was observed. Comparing Pharmacoat with HPC, the former showed a little quicker dissolution velocity than the latter. In the case of former, the time difference for the complete dissolution between the original tablet and the coated tablet was considered to be several minutes. Concerning Pharmacoat and HPC, almost no difference in the dissolution velocity was found between these results and those using other test solution.

The dissolution test results using the JP 1st fluid are shown in the second chart of the figure. In this case, vinyl polymer and acrylic polymer showed almost the same dissolution velocity as Pharmacoat.

In the third through sixth charts of the figure the dissolution test results using Clark-Lubs buffer of pH1.2, pH2.0, pH4.0 and pH6.0 are shown. With an increase in the pH value of the buffer vinyl polymer and acrylic polymer showed slower dissolution velocity. Especially at pH 6.0, no dissolution after 60 minutes (vinyl polymer) or an extremely slower dissolution (acrylic polymer) was observed.

The effect of the pH of the test solution on the dissolution profile of each coating material is summarized in the seventh chart of the figure showing the time required for a 70% dissolution. Pharmacoat showed the most favorable result from the view points of the dissolution velocity being independent of test solution and difference in the dissolution velocity between the original tablet and coated tablet being small.

(Table 10)

An evaluation of the 4.5cP type of Pharmacoat (Pharmacoat-645) was made in comparison with the existing Pharmacoat-606 (6cP) from the viewpoints of basic physical properties, suitable coating conditions and necessary coating time in the actual coating operation. The analytical values of both types of pharmacoat used in the experiment are shown in this table.

(Fig. 2)

The viscosity curves of aqueous solutions for each type of Pharmacoat at 20°C and 40°C are shown. Pharmacoat-645 positioned in between those of Pharmacoat-606 and -603.

(Fig. 3)

The viscosity curves for the solutions of each type of Pharmacoat in a mixture of methylene chloride and ethanol (50:50) at 20°C and 30°C are shown. These solutions generally have a higher viscosity value than those of an aqueous solution at each concentration.

(Fig. 4)

The viscosity curves for the solutions of each type of Pharmacoat in a mixture of water/ethanol (50:50) at 20°C and 40°C are shown. These solutions generally have an intermediate viscosity value between those of an aqueous solution and solution in a mixture of methylene chloride and ethanol (50:50) at each concentration.

(Fig. 5)

The relationship between the tensile strength and the titanium dioxide content of each type of Pharmacoat film is shown. As the percentage of the titanium dioxide is increased the tensile strength of each type of Pharmacoat film is generally decreased. In the case of Pharmacoat-603, the decreasing tendency of the tensile strength with an increase in the titanium dioxide content, is most remarkable. However, the tendency in Pharmacoat-645 is almost the same as that in Pharmacoat-606.

(Fig. 6)

The relationship between elongation and the titanium dioxide content of each type of Pharmacoat film is shown. Pharmacoat-603 especially shows low elongation which sometimes may cause film defects in the actual tablet coating. The elongation of the Pharmacoat-645 film is lower than that of Pharmacoat-606, and there doesn't seem to be much need for concern for film defects considering the actual elongation values.

(Fig. 7)

The dissolution time for each type of Pharmacoat film is shown. There is almost no difference in the dissolution time between the film of Pharmacoat-606 and -645. Evidently though, Pharmacoat-603 shows a shorter dissolution time than Pharmacoat-606 and -645.

(Fig. 8)

Water vapor permeability of each type of Pharmacoat film is shown. As a test condition, the humidity of one side of the film was set to a uniform 0% RH and that of the other side was changed by using every kind of saturated salt solution. Our conclusion is that there is no difference in the water vapor permeability among films of Pharmacoat-606, -645 and -603.

(Fig. 9)

Based on the assumption that the surface roughness of a coated tablet may be closely connected with the sprayed mist of the coating solution, the effects of various factors on the particle size of the sprayed mist of Pharmacoat solutions were studied. This figure shows the effect of the viscosity of a coating solution on the particle size of sprayed mist in the cases of Pharmacoat-606 and -645 respectively. As for the particle size, those values at two percentage

points (50% and 90%) of the undersize volume distribution were obtained respectively. In the relationship curve between the viscosity of the solution and the particle size of sprayed mist, that of Pharmacoat-645 lies at a slightly lower position from that of Pharmacoat-606 on the whole.

(Fig. 10)

This figure shows the effect of a concentration of the solution on the particle size of sprayed mist in the cases of Pharmacoat-606 and -645 respectively. As the concentration of the solution is increased the particle size of the sprayed mist is at first, until around a 2% concentration, decreased because of the decrease in the surface tension of the solution, and then it increases by the influence of the viscosity increase. As shown in the figure, the particle size of a solution from Pharmacoat-645 is distinctly smaller than that from Pharmacoat-606 at every concentration.

(Fig. 11)

This figure shows the effect of a spraying distance on the particle size of sprayed mist when using a 10% solution of Pharmacoat-645. This figure suggests that the minimum spraying distance at which the particle size reaches a steady state particle size will be dependent on the spray air velocity and/or spray solution velocity.

(Fig. 12)

The surface roughness of a coated tablet with Pharmacoat was evaluated by using a surface texture measuring instrument. The trade name of the instrument is Surfcom 550A, manufactured by Tokyo Seimitsu Co., Ltd. This figure shows a sample of a chart for the surface roughness of a coated tablet. As shown in the figure, the maximum height (RT) and center-line mean roughness (Ra) are measured for the evaluation of the surface roughness.

(Fig. 13)

The effect of the concentration of the solution of Pharmacoat-645 on the surface roughness of a coated tablet is shown. As the concentration of the solution is increased the surface roughness increases steadily.

(Fig. 14)

The effect of the spray solution velocity on the surface roughness of a coated tablet is shown. There is a tendency that the surface roughness increases rapidly as the spray velocity of the solution is increased past a certain point.

(Fig. 15)

Two examples of the change in a surface roughness during the coating are shown. The surface

roughness at first increases, and then it shifts to a fixed level with an increase in the coating amount.

(Table 11)

In order to confirm the usefulness of Pharmacoat-645 in the actual applications, coating experiments were made on both a small scale and a production scale. The formulations of tablets and the coating solution used in the experiments are shown in the table.

(Table 12)

The coating conditions in the small scale experiment are shown.

(Table 13)

The coating conditions on a production scale are shown.

(Fig. 16)

The change in the operational parameters during coating in the small scale experiment is shown. In this case, a reduction of approximately one fourth of the coating time required for Pharmacoat-606 coating could be achieved by changing to Pharmacoat-645.

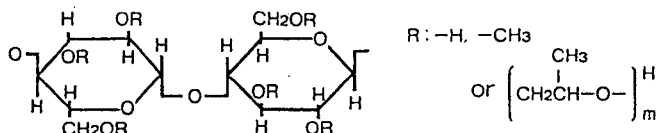
(Fig. 17)

The change in the operational parameters during coating on a production scale experiment is shown. In this case, a reduction of approximately one third of coating time required for Pharmacoat-606 coating could be achieved by changing to Pharmacoat-645.

Table 1. Hydroxypropyl Methylcellulose

Nonproprietary Name	Hydroxypropylmethylcellulose 2910 (JP)
Chemical Name	Cellulose Hydroxypropylmethylether
Abbreviation	HPMC
Codex	JP. USP. EP

Structural Formula



Description

Soluble in cold water. Aqueous solution gels at around 60°C. Insoluble in alcohol. Soluble in mixtures of alcohol/water and alcohol/methylene chloride. Exhibit an excellent film forming property, low spinnability and good printability.

Commercial Availability

Pharmacoat 603, 645, 606, 615 (Shin-Etsu Chemical)
E-5, E-15 (Dow Chemical)

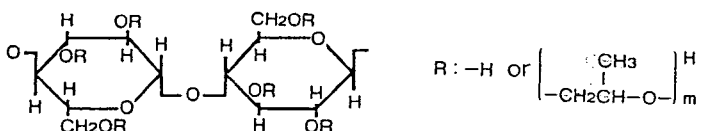
Method of Manufacture

Alkali cellulose prepared from cellulose is treated with methyl chloride and propylene oxide to produce methylhydroxypropyl ether of cellulose.

Table 2. Hydroxypropyl Cellulose

Nonproprietary Name	Hydroxypropylcellulose (JP)
Chemical Name	Cellulose, Hydroxypropyl ether
Abbreviation	HPC
Codex	JP. USP. EP

Structural Formula



Description

Soluble in water below 38°C. Soluble in ethanol, methanol and isopropyl alcohol (95%). Swells in acetone and insoluble in ether. Characteristically soluble in simple alcohol. Exhibits an excellent film forming property, low softening point and low spinnability.

Commercial Availability

HPC-SL HPC-L (Nippon Soda)
HPC-LEP, LEG (Hercules)

Method Manufacture

Alkali cellulose prepared from cellulose is treated with propylene oxide to produce hydroxypropyl ether of cellulose.

Table 5. Tablet Formulation

VB ₂	3.8mg
lactose	144.4mg
starch	36.1mg
HPC	3.8mg
St-Mg/Talc	1.9mg
<hr/>	
Total	190.0mg

Table 6. Tablet Properties

diameter	8mmØ 190mg/T
hardness	4.8kg/cm ²
friability	0.24%
disintegration time	8'57" JP 1st fluid
	9'23" water
dissolution time	15min JP 1st fluid
(100%)	15min water

Table 7. The Formulation of the Coating Solution

HPMC

Pharmacoat		
606	6%	
water		94%

HPC

HPC-LEP	6%
PEG6000	0.6%
water	93.4%

Vinyl polymer

AEA	6%
ethanol	47%
acetone	47%

Acrylic polymer

Eudragit E-100	6.0%
talc	1.8%
ethanol	86.2%
water	6.0%

Table 8. Coating Conditions

Apparatus small-sized side-vented pan
 Pan size 30cm ϕ
 Revolution 14--18rpm
 Spray gun nozzle diameter 0.8mm ϕ 1/8 J type (Spraying System Co.)

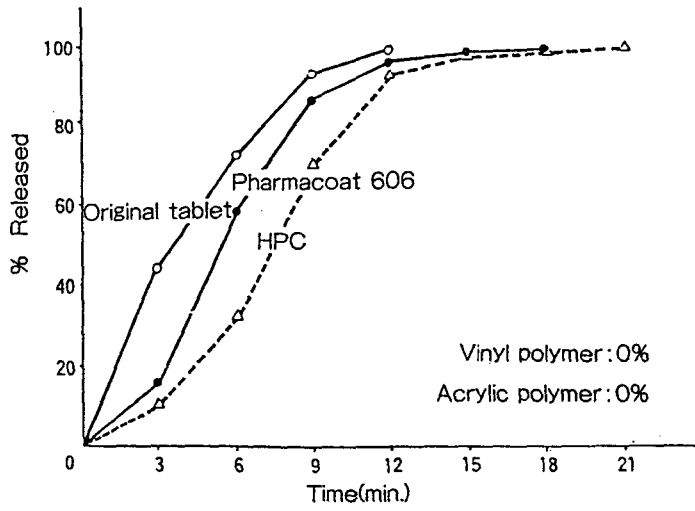
	Pharmacoat 606	HPC	Vinyl polymer	Acrylic polymer
inlet drying air temperature	72 $^{\circ}$ C	72 $^{\circ}$ C	46 $^{\circ}$ C	46 $^{\circ}$ C
spray speed	6g/min.	4g/min.	12g/min.	11g/min.
tablet bed temperature	43 $^{\circ}$ C	43 $^{\circ}$ C	35 $^{\circ}$ C	37 $^{\circ}$ C
tablet charge	1200g	1200g	1200g	1200g
coating time	135min.	200min.	67min.	70min.
quantity of coating material applied	4%	4%	4%	4%
disintegration time 1st fluid	8' 27"	12' 30"	9' 07"	8' 31"
(n=6) water	9' 50"	14' 24"	>120'	>120'

Table 9. Dissolution Test

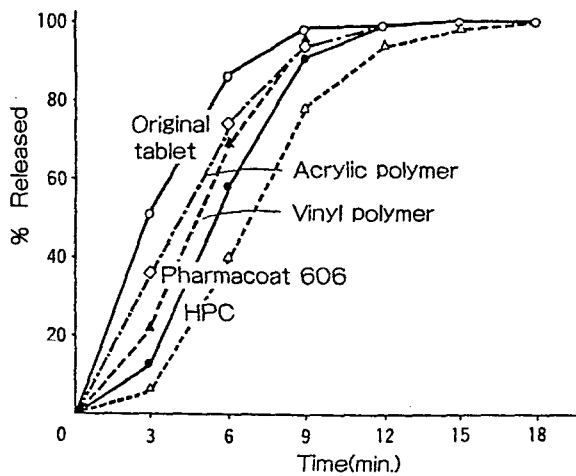
Rotational speed of paddle	100rpm
Volume of test solution	900ml
Amount of sample	4 tablets(15.2mg riboflavin)
Determination method	UV method
Test solution	Clark Lubs buffer solution pH 1.2, 2.0, 4.0, 6.0 JP 1st fluid(pH1.2) water (deionized water)
Operation period	1 hour

Fig. 1. Effect of pH on the Dissolution Rate of VB₂ Tablets Coated with Various Coating Materials

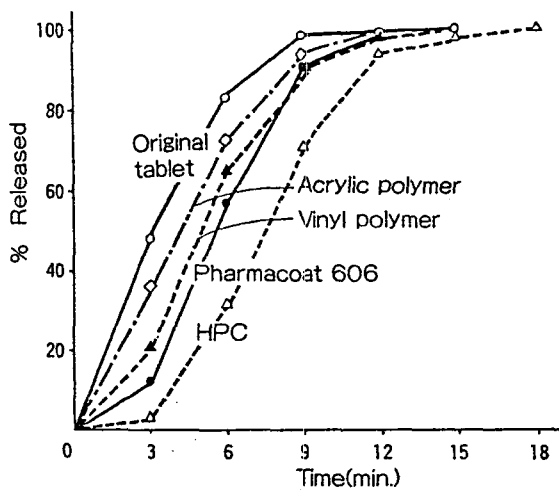
Test solution: water



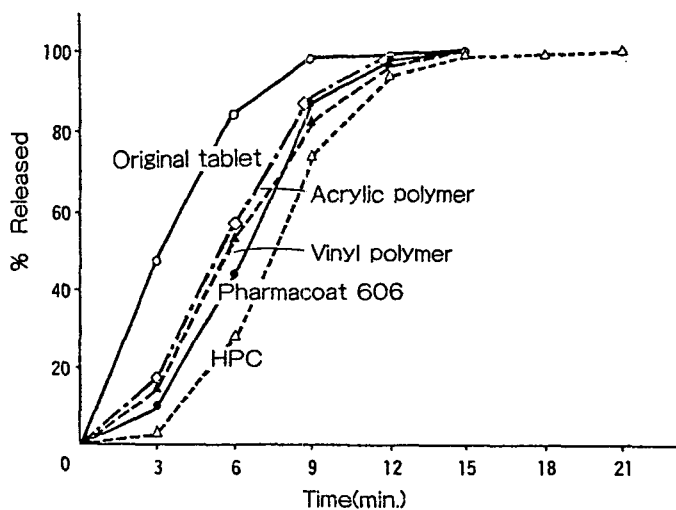
Test solution: JP 1st fluid



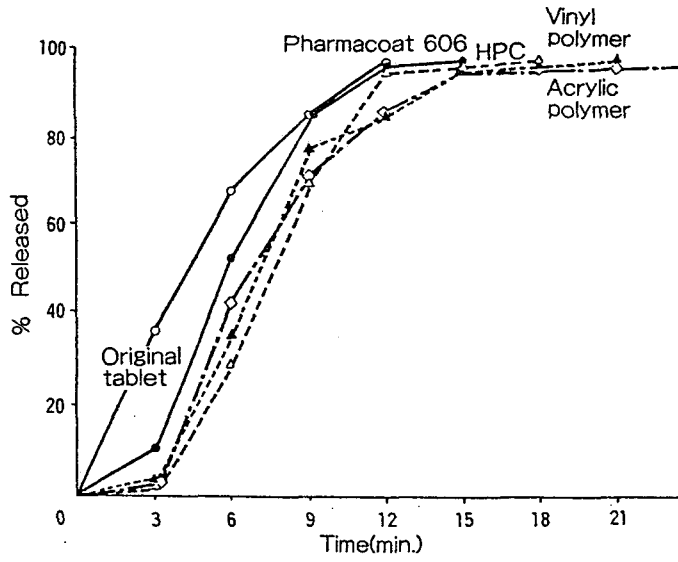
Test solution: pH1.2(Clark-Lubs)



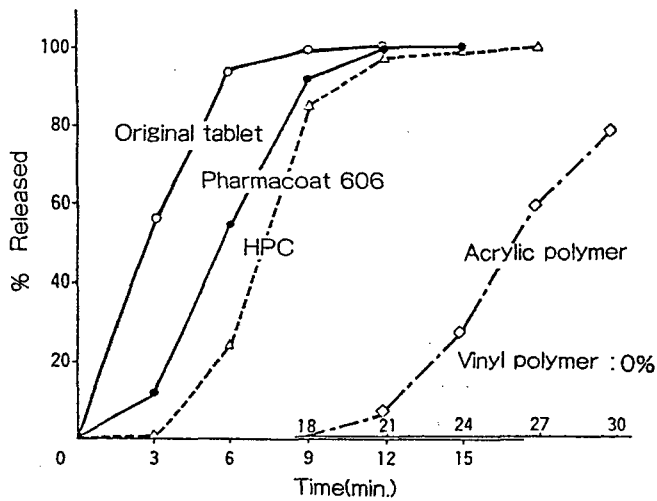
Test solution: pH2.0(Clark-Lubs)



Test solution: pH4.0(Clark-Lubs)



Test solution: pH6.0(Clark-Lubs)



The time required for 70% dissolution in various test solutions

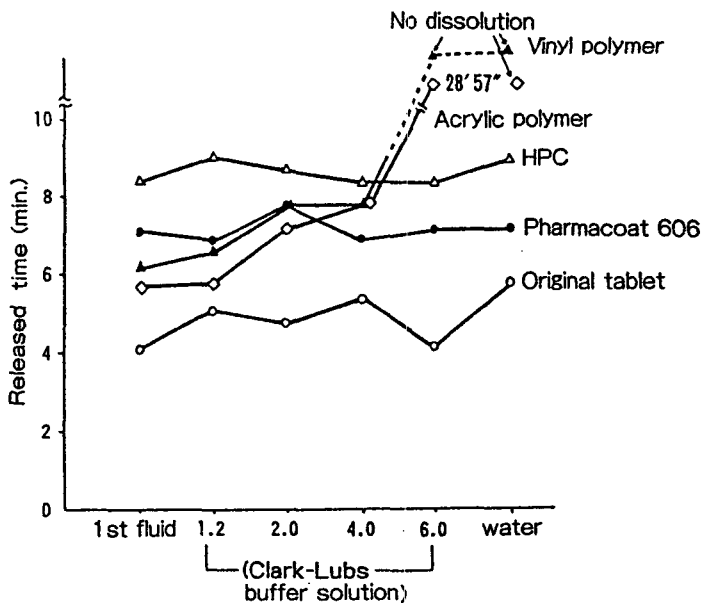


Table 10. Analytical Values of Pharmacoat Used in the Coating Experiments

Type (Lot No.)	Pharmacoat 645 (63-018)	Pharmacoat 606 (63-186)
Viscosity	4.64cSt	5.55cSt
Loss on drying	1.3%	1.9%
Residue on ignition	0.55%	0.52%
Methoxyl content	28.9%	29.2%
Hydroxypropoxyl content	9.0%	9.2%
pH	6.9%	7.2%
YI*(powder)	10.6	10.4.
(solution).	10.2	7.5

* YI : yellow intensity

Fig. 4. Viscosity Curve of Pharmacoat

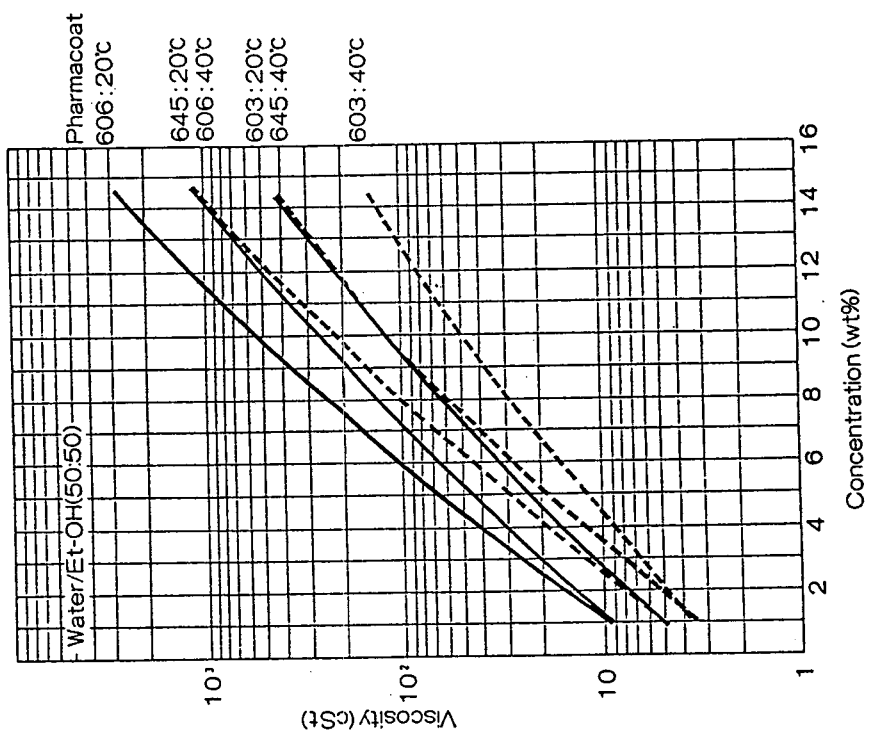


Fig. 5. The Relationship between the Tensile Strength and the TiO₂ Content of Pharmacoat Film

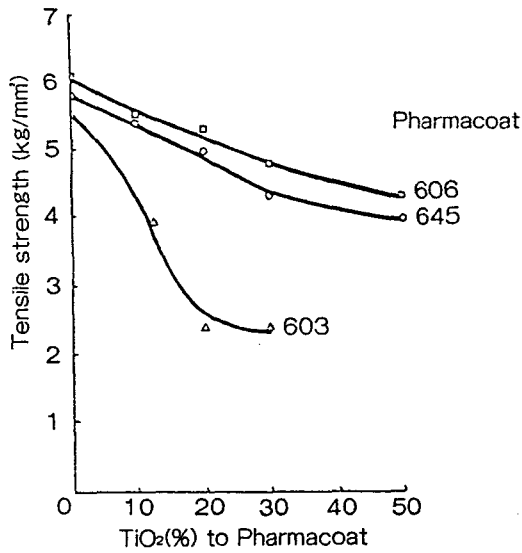
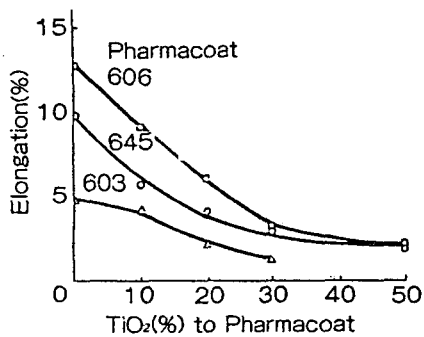


Fig. 6. The Relationship between Elongation and the TiO₂ Content of Pharmacoat



Apparatus: Shimazu Autograph (DDS-10T-S)

Test specimen: 100 μ m in thickness, #1 dumbbell

Conditioning of sample: 3 days at 25 $^{\circ}$ C, 50% RH

Stress rate: 10mm/min.

Fig. 7. The Dissolution Time of Pharmacoat Film

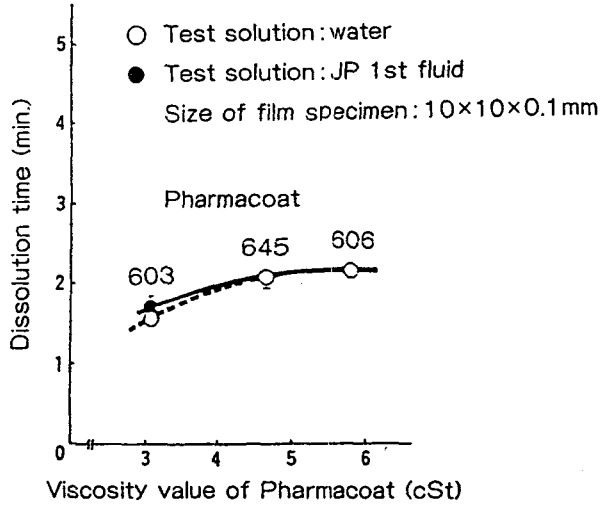


Fig. 8. The Water Vapor Permeability of Pharmacoat Film at 25° C

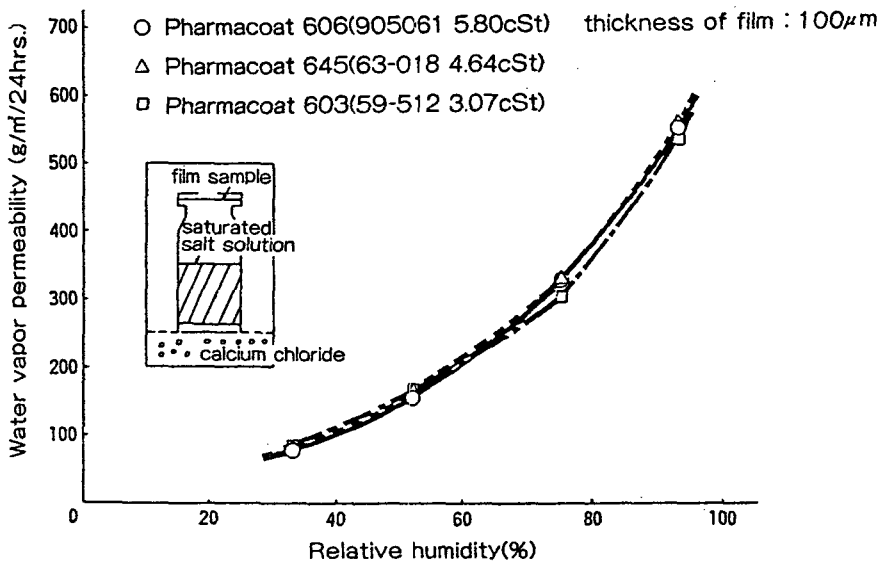


Fig. 9. The Effect of Viscosity on Particle Size of Sprayed Mist

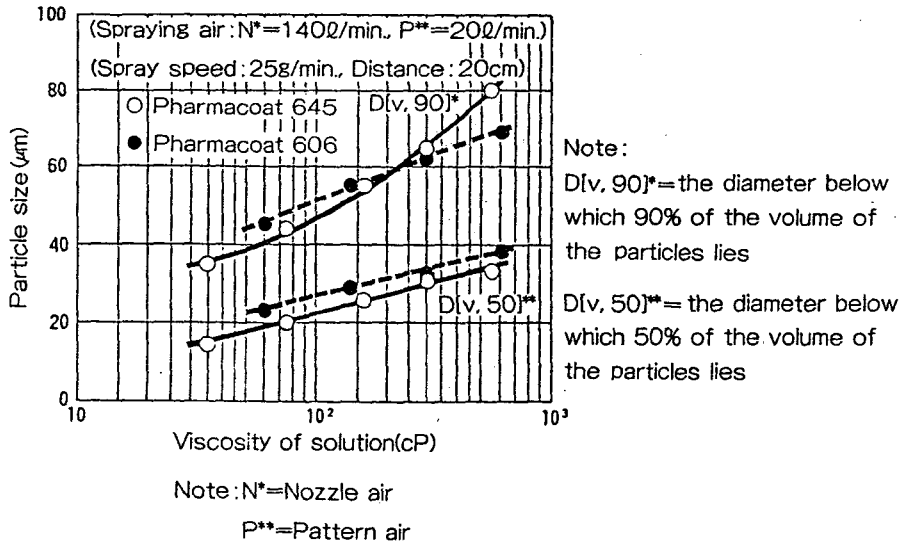


Fig. 10. The Effect of Solution Concentration on the Particle Size of Sprayed Mist

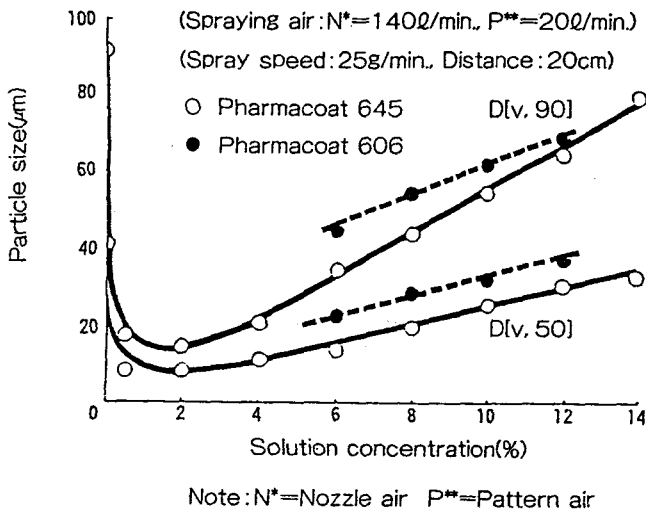


Fig. 11. The Effect of the Spraying Distance on the Particle Size of Sprayed Mist

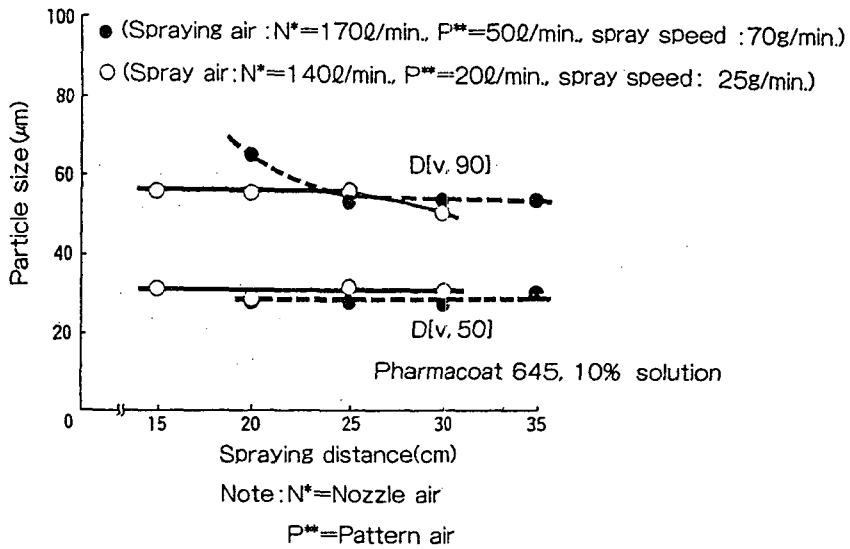


Fig. 12. A Sample of a Chart for the Surface Roughness of a Coated Tablet

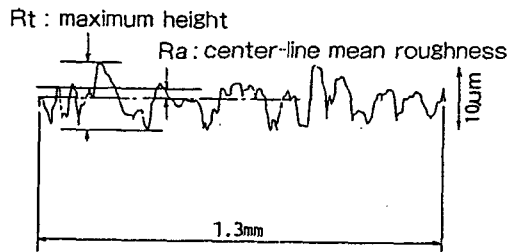


Fig. 13. The Effect of Concentration of Pharmacoat 645 Solution on the Surface Roughness of a Coated Tablet

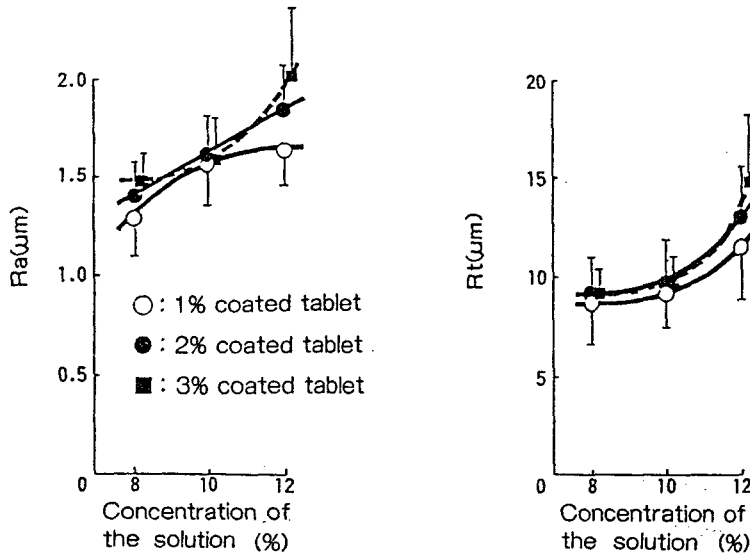


Fig. 14. The Effect of Spray Speed on Surface Roughness of a Coated Tablet

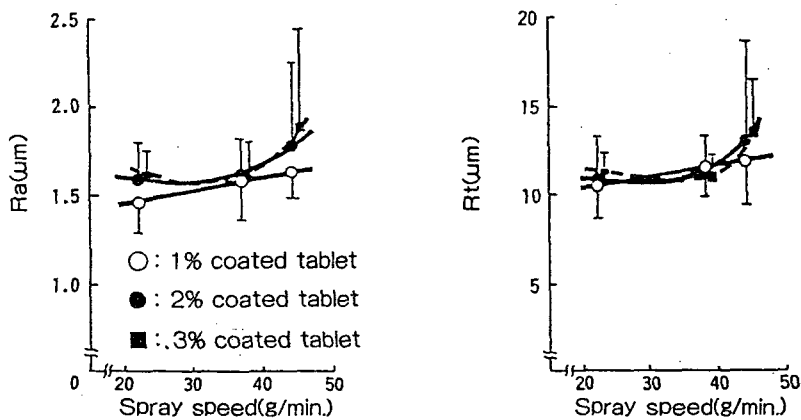
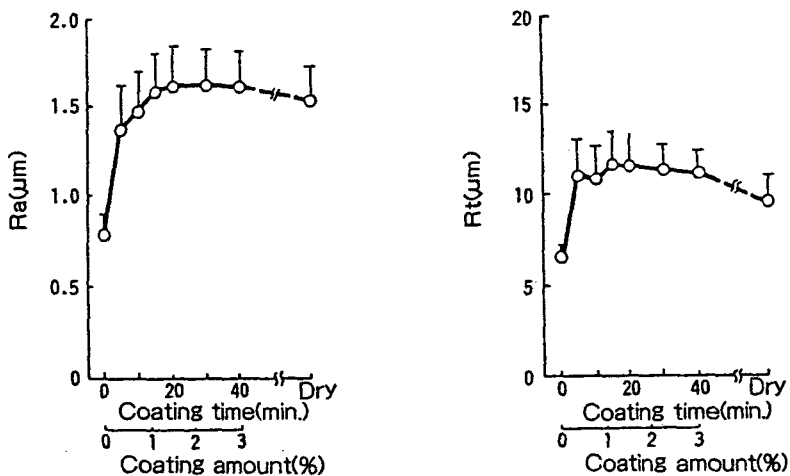


Fig. 15. The Change in the Surface Roughness during Coating

(1) Pharmacoat 645, 10% concentration, spray speed 38g/min.



(2) Pharmacoat 606, 8% concentration, spray speed 38g/min.

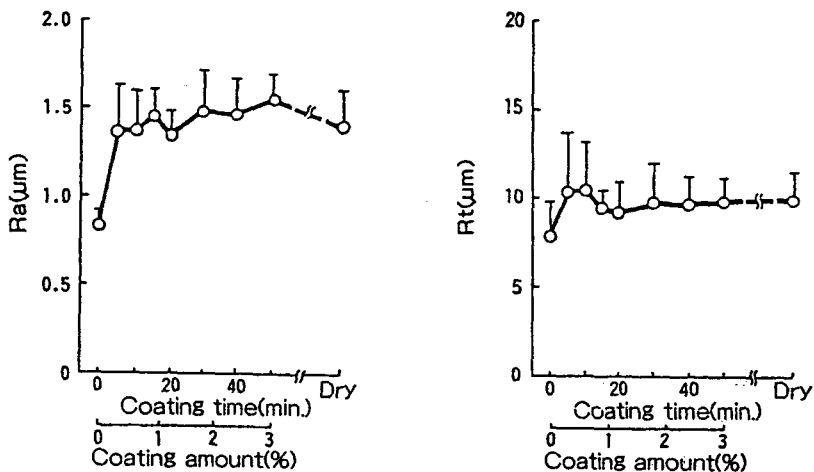


Table 11. The Formulations of Tablets and the Coating Solution

Tablet formulation

Fast Flo lactose	79.5parts
Constarch	15.0
LH-11	5.0
Mg-Stearate	7.5

Total 100.0parts

Tablet properties

6.5mm ϕ , 5.0mmR,	120mg/Tab
hardness	11.6kg(R=4.3kg)
disintegration time	2'30" (R=42")
moisture content	3.3%

The formulation of the coating solution

Pharmacoat 606		Pharmacoat 645	
Pharmacoat 606	6parts	Pharmacoat 645	10parts
water	94	water	90
Total	100parts	Total	100parts

Table 12. Coating Conditions (small scale experiment)

Apparatus	New Hicoater HCT-48N (Freund Industrial)	
Tablet charge	5kg	
Spray gun	one ATF, nozzle diameter 1.2mm ϕ	
Spraying air	150 ℓ /min. (2.0kg/cm 2)	
Distance of gun from surface of tablet bed	16cm	
Drying air direction	parallel flow	
	Pharmacoat 606	Pharmacoat 645
Drying air	25 m^3 /min.	←
Spray speed	30g/min.	←
Inlet air temperature	70 $^{\circ}\text{C}$	←
Outlet air temperature	44 $^{\circ}\text{C}$	45 $^{\circ}\text{C}$
Tablet bed temperature	39 $^{\circ}\text{C}$	40 $^{\circ}\text{C}$
Pan revolution	16rpm	←
Quantity of coating solution applied	3% as Pharmacoat	←
Concentration of Coating solution	6%	10%
Coating time	83min.	50min.
Postdrying	30minute exposure in the pan under inlet air of 50 $^{\circ}\text{C}$	

Table 13. Coating Conditions(production scale experiment)

Apparatus	NEW HICOATER HC-130N (Freund Industrial)	
Tablet charge	120kg	
Spray gun	three AT, nozzle diameter 1.2mm ϕ	
Spraying air	atomizing air	170l/min.
	atomizing air +	
	pattern air	250l/min.(at 5.3kg/cm ²)
Distance of gun from surface of tablet bed	30cm	
Drying air direction	parallel flow	
	Pharmacoat 606	Pharmacoat 645
Drying air	15m ³ /min.	←
Spray speed	210g/min. (70g/min./gun)	←
Inlet air temperature	80 $^{\circ}$ C	←
Outlet air temperature	46 $^{\circ}$ C	47 $^{\circ}$ C
Tablet bed temperature	46 $^{\circ}$ C	47 $^{\circ}$ C
Pan revolution	8rpm.	←
Quantity of coating solution applied	3% as Pharmacoart	←
Concentration of coating solution	6%	10%
Coating time(spraying time)	286min.	171min.
Postdrying	for 30minutes in the pan under inlet air of 50 $^{\circ}$ C	

Fig. 16. The Change in Operational Parameters during Coating (HCT-48N)

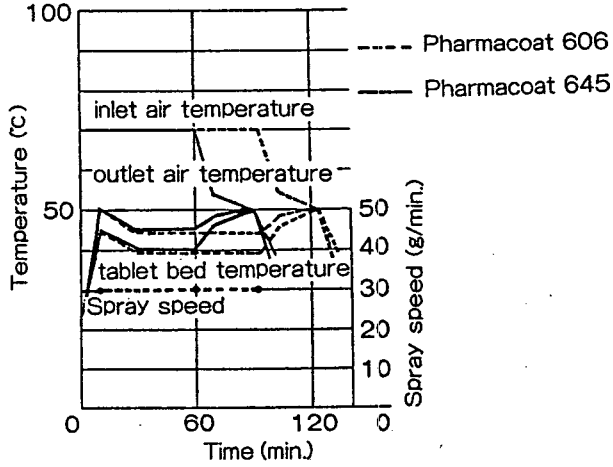


Fig. 17. The Change in Operational Parameters during Coating (HC-130N)

