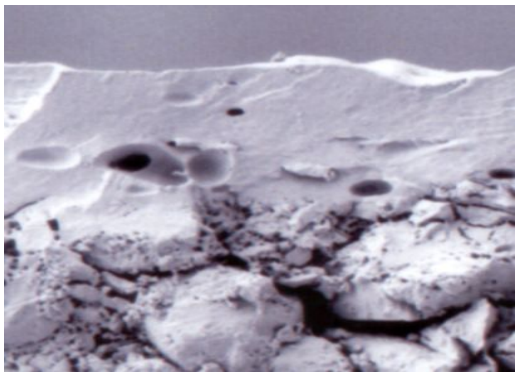
Polyvinyl alcohol-Acrylic acid-Methyl methacrylate copolymer

POVACOAT®

~The characteristics of POVACOAT and its application~



Daido Chemical Corporation

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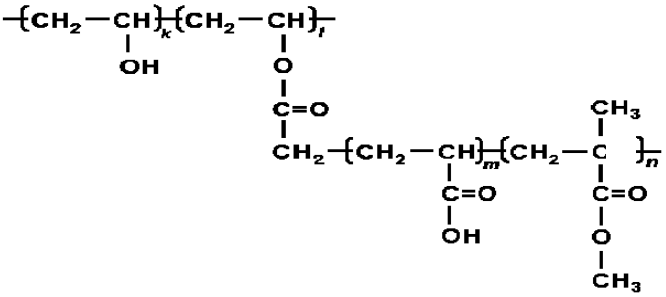
< *Introduction* >

POVACOAT (Polyvinyl alcohol/ Acrylic acid/ Methyl methacrylate copolymer) is a novel pharmaceutical excipient. The chemical structure is shown in Fig.1.

POVACOAT is supplied as Type R with the molecular weight of 200,000 and Type F with the molecular weight of 40,000. Type R is being applied to hard capsule (PONDAC) material and Type F is being done as a material for film coating, wet granulation binder and solid dispersion matrix, etc.



Drug Master File No. 18033

Fig.1 Chemical structure of POVACOAT

< *Physicochemical properties of POVACOAT* >

○ Solubility: POVACOAT is soluble in water. About 30% of ethanol can be added but the substance becomes insoluble at higher concentrations.

○ Viscosity: As seen in Fig.2, a linear relationship is shown between viscosity in log and polymer concentration.

○ Hygroscopic property: POVACOAT is hygroscopic and the water content increases with the increase of the relative humidity.

○ Thermo stability: POVACOAT is thermo stable between about 130°C and 220°C but is degraded above 220°C. Glass transition temperature (Tg) is observed between about 60°C and 80°C.

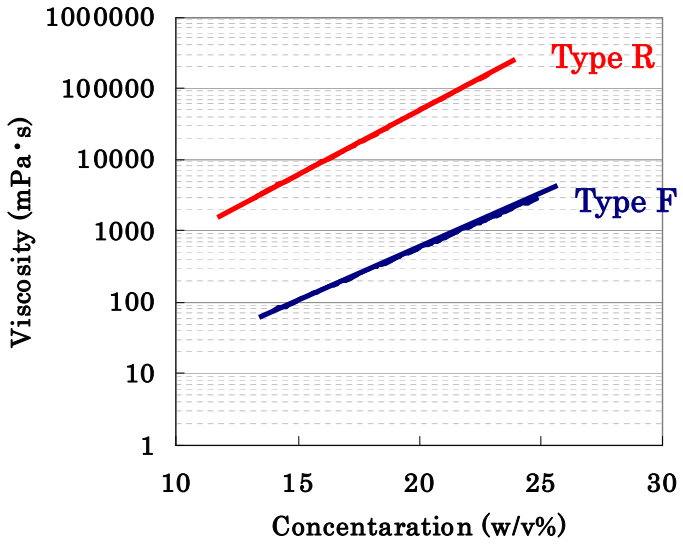


Fig.2 Relationship between polymer concentration and viscosity

< Physical properties of POVACOAT >

1) Oxygen permeability

Table 1 shows the results of oxygen permeability tests. Permeability of oxygen differs considerably and this is very remarkable characteristics of POVACOAT membrane. Since POVACOAT can form a dense film resulting from strong hydrogen bonding, the diffusion coefficient of oxygen is much lower than that of other polymer film. As a result, oxygen molecules hardly pass the film.

Table 1 Results of the oxygen permeability test

Film	Oxygen (mol/m^2·sec·Pa)
Type R	1.80×10^{-15}
Type F	3.00×10^{-15}
Gelatin	3.35×10^{-6}
HPMC	8.13×10^{-4}

Measuring method; manometric visual determination (ASTM D1434)

Measurement condition; 23℃, Film thickness; 100μm

2) Moisture permeability

In order to evaluate the moisture permeability, the aluminum casing with the isolated film which was stuck on the opening part (40mm×40mm) was used as seen in Fig.3. The aluminum casing was heat sealed, after 3.0g of calcium chlorides was put into the inside as a moisture absorption agent. The increase in weight per 24 hours of the calcium chloride under various relative humidity was measured, and the moisture permeability coefficient was calculated. The result is shown in Fig.4.

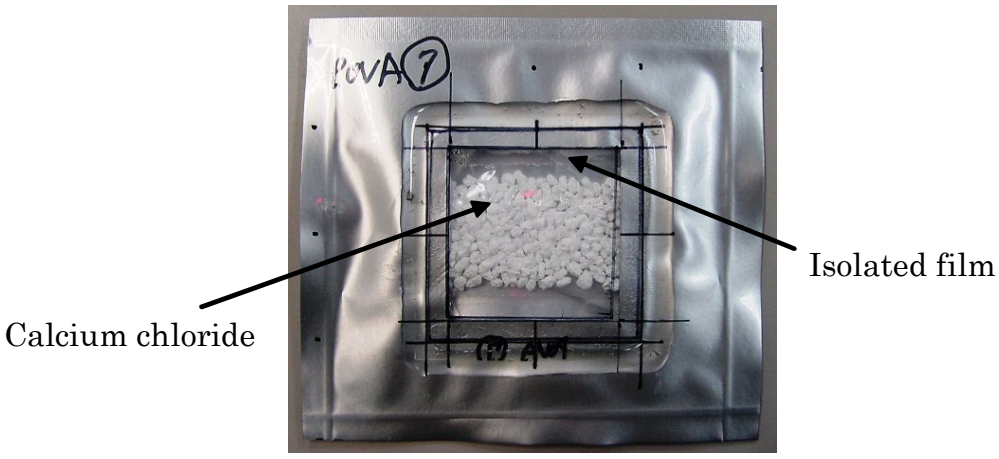


Fig.3 Appearance of test sample

In the case of the hydroxypropylmethylcellulose (HPMC), the moisture permeability coefficient is gradually increased according to relative humidity. On the other hand, that of POVACOAT showed sigmoid type changes.

In figure the result of the addition of talc is shown together. It is clear that POVACOAT has a good performance against moisture barrier under various humidity conditions.

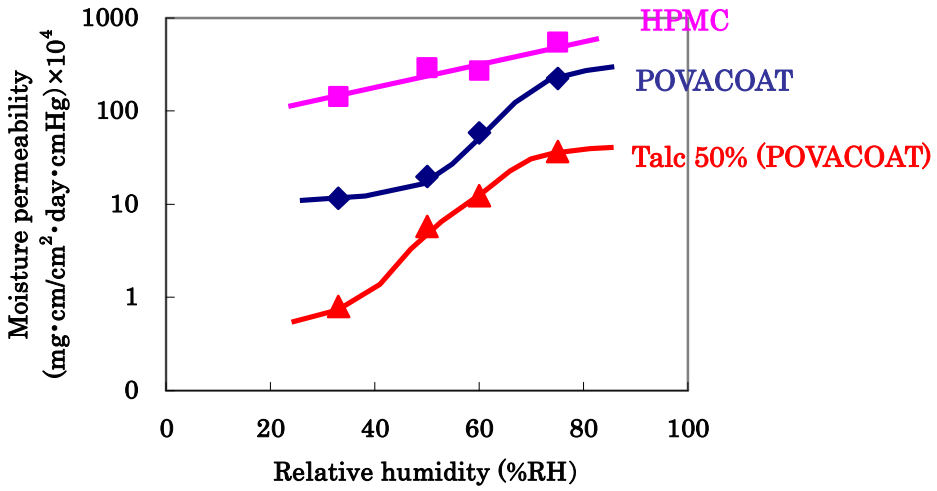


Fig.4 Plots of moisture permeability coefficient against relative humidity

3) Strength and elongation of film

Table 2 and 3 shows the strength and elongation of casting films. The strength for tear of the films decreases with the increase in water content but this decreasing tendency is not so obvious for POVACOAT Type F. With regard to elongation, on the other hand, it can be seen that POVACOAT stretches very well in comparison to other materials.

Table 2 Results of the strength (N/mm²) for tear of the casting films

Film	25°C / 50%RH	25°C / 75%RH
Type R	32.2	24.2
Type F	25.0	20.0
Gelatin	55.6	16.7
HPMC	30.8	14.7

Table 3 Results of the elongation in % of the casting films

Film	25°C / 50%RH	25°C / 75%RH
Type R	170	312
Type F	50	100
Gelatin	5.1	11.2
HPMC	5.1	3.2

4) **High pigment volume concentration (PVC) film**

The strengths and elongations of POVACOAT films by varying the contents of added TiO_2 are plotted in Fig.5 and tabulated in Table 4, respectively.

It has been found that over 30 wt% TiO_2 the strength of POVACOAT film is decreased under 40%RH but it may be increased to 50 wt% while maintaining its function as a film under a high humidity condition. In the respect of elongation, up to 50% of TiO_2 high elongation property of film is maintained. POVACOAT film can be said to a called high PVC film. This high PVC of POVACOAT is considered to be effective when it is used as a film coating.

Photo.1 shows the appearances of aqueous POVACOAT solution dispersed TiO_2 and that of HPMC after 24 hours. POVACOAT shows a very favorable dispersion. This property of POVACOAT will helps well film coating operations.

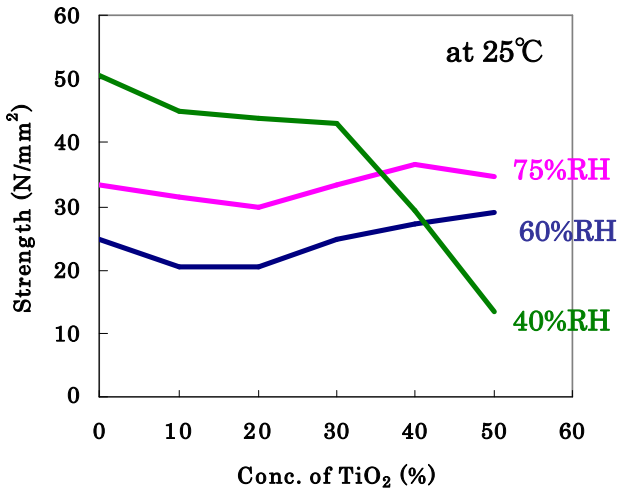


Fig.5 Relationship between concentration of TiO_2 and strength of films

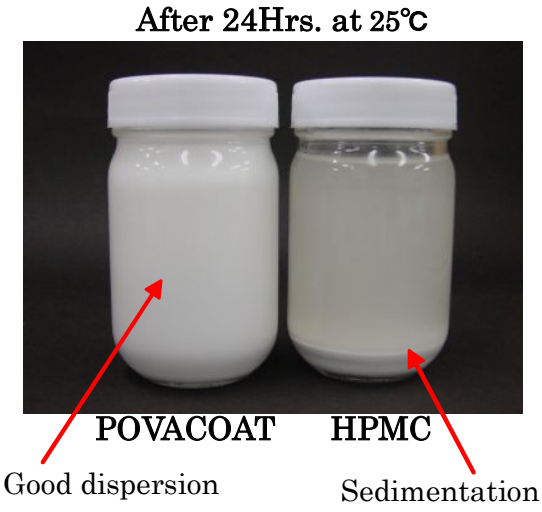


Photo.1 Dispersion of TiO_2

Table 4 Elongation in % of the film with added amounts of TiO_2

		Added amounts of TiO_2 (w/w%)					
Film	Storage condition	0	10	20	30	40	50
POVA	25℃60%RH	29.4	22.0	27.2	38.1	37.2	20.9
	40℃75%RH	59.7	60.4	63.1	73.9	72.2	51.6

Film thickness; 50μm

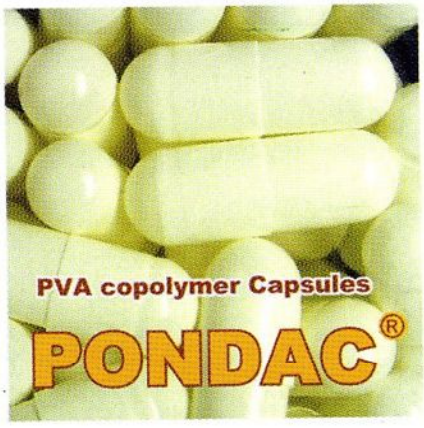
<Application of POVACOAT>

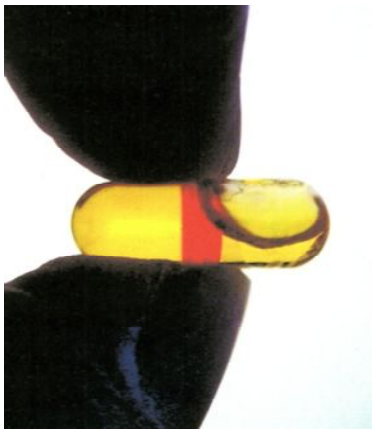
1) Hard capsules (PONDAC)

Characteristics of PONDAC are oil resistance and oxygen barrier. PONDAC has following characteristics. This table shows comparison of 3 capsule types. The substance allows filling of PEG 400 (macrogol) set as a design goal and is also characterized by less generation of static electricity.

Table 5 Characteristics of PONDAC

Property	PONDAC	Gelatin	HPMC
Water content	4-6 %	13-15 %	2-5 %
Gloss	Yes	Yes	Low
Water vapor permeability	Low	Low	Low
Oxygen permeability	**Very Low**	Low	High
Maillard reaction with filled substance	No	Yes	No
Light degradation	No	Yes	No
Protease degradation	No	Yes	No
Static electricity	Weak	Strong	Weak
Filling of macrogol 400	**Possible**	Impossible	Impossible
Filling of Tween 80	**Possible**	Impossible	Impossible





2) Film coating

2-1) Oxygen barrier

The result shows comparison with HPMC film coating using vitamin C, which is degraded by oxygen, as a model drug. (Fig.6 The amount of coating is 10 %.) In comparison to ascorbic acid tablets coated with HPMC, deterioration of the tablets coated with POVACOAT was prevented to the same degree as that obtained by nitrogen substitution indicating that oxygen barrier property was effective for film coating similarly to casting film. (See Table 1)

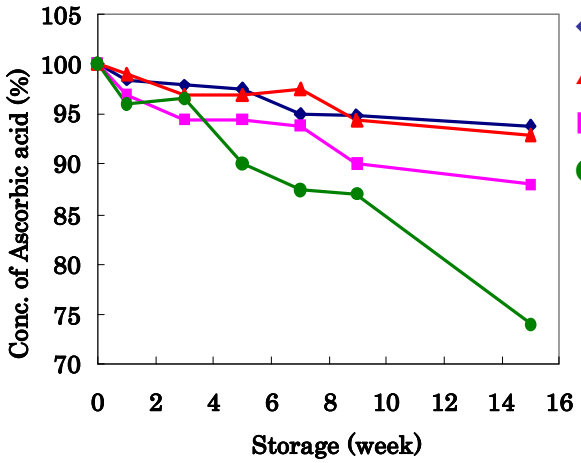


Fig.6 Stability of ascorbic acid

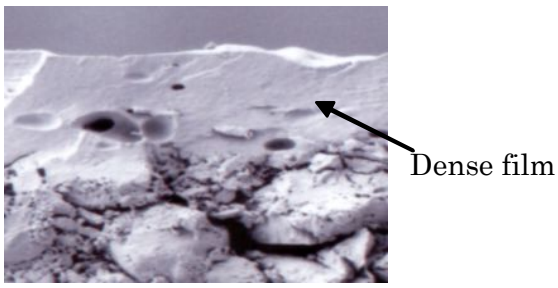


Photo.2 Cross section of POVACOAT film

2-2) Whisker prevention effect

Whiskers appearing as needle-like crystals of the drug on the tablet surface are a well-known problem. When occurrence of whiskers was compared by film coating preparations containing caffeine and potassium guaiacolsulfonate, typical examples of such formulations, HPMC coating could not prevent occurrence of whiskers but whiskers were not observed with POVACOAT film-coating. It was considered that the dense film of POVACOAT was the factor that prevented occurrence of whiskers.

Noncoated tablets　Tablets coated by HPMC　Tablets coated by POVACOAT

Photo.3 Whisker prevention effect

2-3) Elongation of film

Tablets of OTC drugs combined with sodium chondroitin sulfate sometimes break as a result of swelling due to absorption of moisture. An example of application of POVACOAT to such a formulation is shown. Even for a formulation which breaks with existing HPMC as shown in the photograph, POVACOAT film-coated tablets did not break because POVACOAT stretched to cover swelling of the tablets.

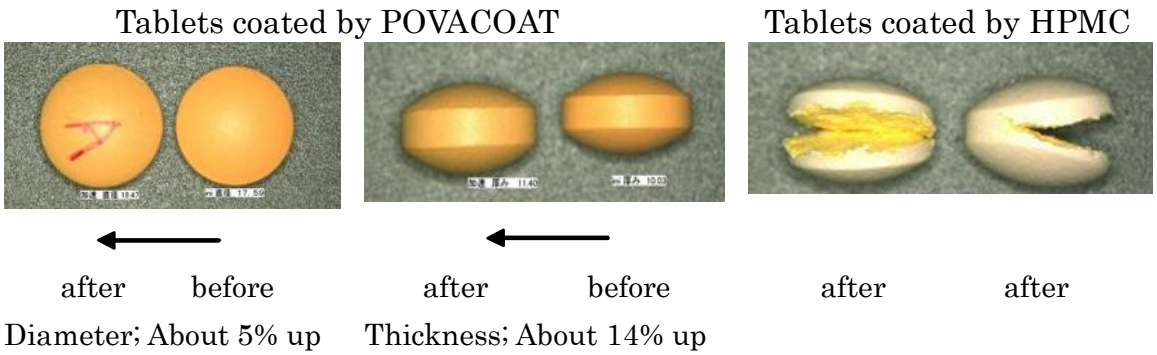


Photo.4 Breakage by swelling of the tablet under 40℃75%RH 1week

3) Wet granulation binder

3-1) Preparation of binder liquid

In general, re-dispersion and solubilization process of aqueous polymer is time-consuming one. It's easy to prepare the POVACOAT aqueous solutions for film coating or granulation binder liquid under room temperature.

The viscosities of obtained aqueous solutions of POVACOAT and other polymer are listed in Table 6. The viscosity of POVACOAT solution is smaller than HPC and higher than PVP.

Table 6 Viscosity (mPa・s) comparison among POVA, HPC-L, HPC-SL, and PVP

Conc. (w/v%)	POVA	HPC-L	HPC-SL	PVP(K-30)
6	7.1	82	33.5	4.0
9	21	375	83	6.0
12	63.5	975	260	8.0
18	370	12,740 *)	1,940 *)	16.0 *)
22.2	1,525	72,100 *)	8,140 *)	26.5 *)

*); estimated values by extrapolation

3-2) Granulation by using POVACOAT

In order to evaluate the applicability of POVACOAT as a granulating binder, granulation torque measurements were preliminarily curried out by using a Mixer Torque Rheometer (MTR).Lactose/corn starch; 7/3 was used for a placebo formulation and HPC-L was done as a comparison. Results of measurements are shown in Fig 7-a).

Binder liquid amounts indicated torque maximum is called as a plasticity limit (PL). Fig.7-a) shows a difference between PL of POVACOAT and one of HPC-L, suggests that in POVACOAT case, an effective granule growth is occurred at a less amounts of binder than HPC-L. For comparison among various granulation, normalized WB (WBR: arbitrary binder liquid amount versus PL) is well used as a comparison parameter. Fig.7-b) shows the plots of D50 at various binder amounts by using such a WBR. It is well-known from the studies on unit operation of granulation that granules growth (D50) is effectively occurred among 0.5~0.85 of WBR. It was found that mean particle size (D50) is sharply increase at about 0.6 of WBR in both cases of POVACOAT and HPC-L from Fig.7-b).

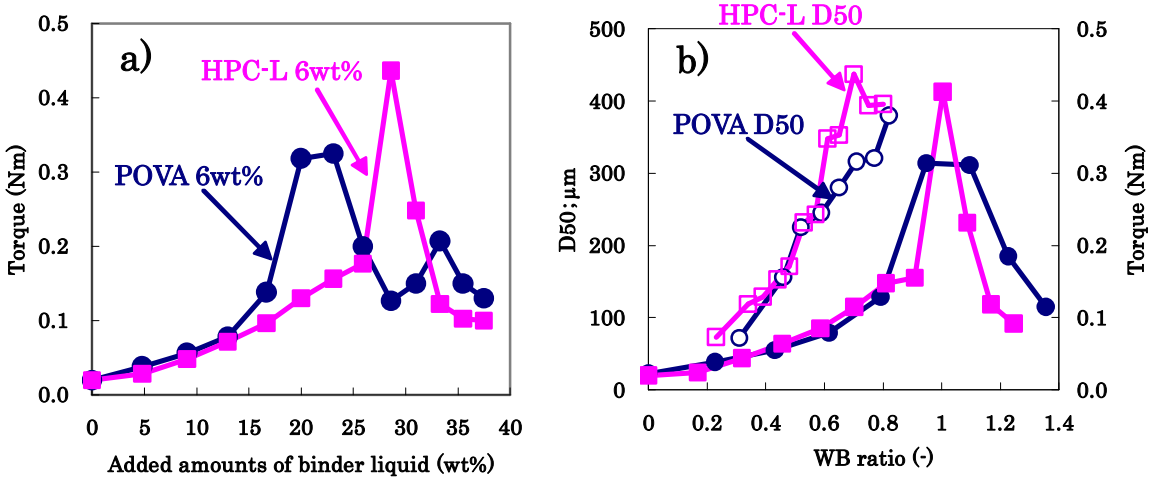


Fig.7 Torque pattern a) and granulation growth (D50) b) with added amounts of binder liquid

The PL values of drug containing formulations cases were summarized in Fig.8. POVACOAT binder was suggested to be effective too in drug containing formulations.

It is assumed that these less binder liquid content of POVACOAT is resulting from a good wetability.

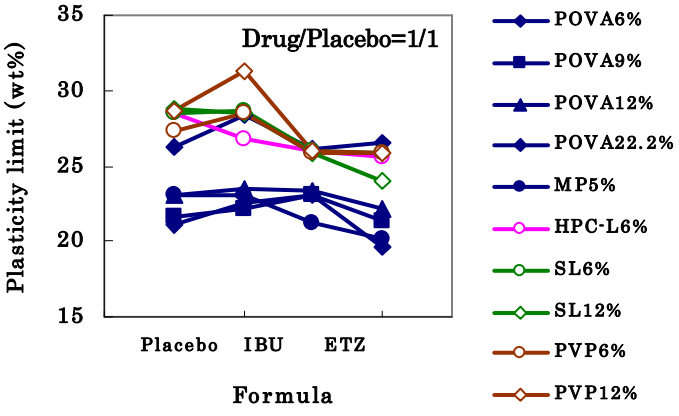
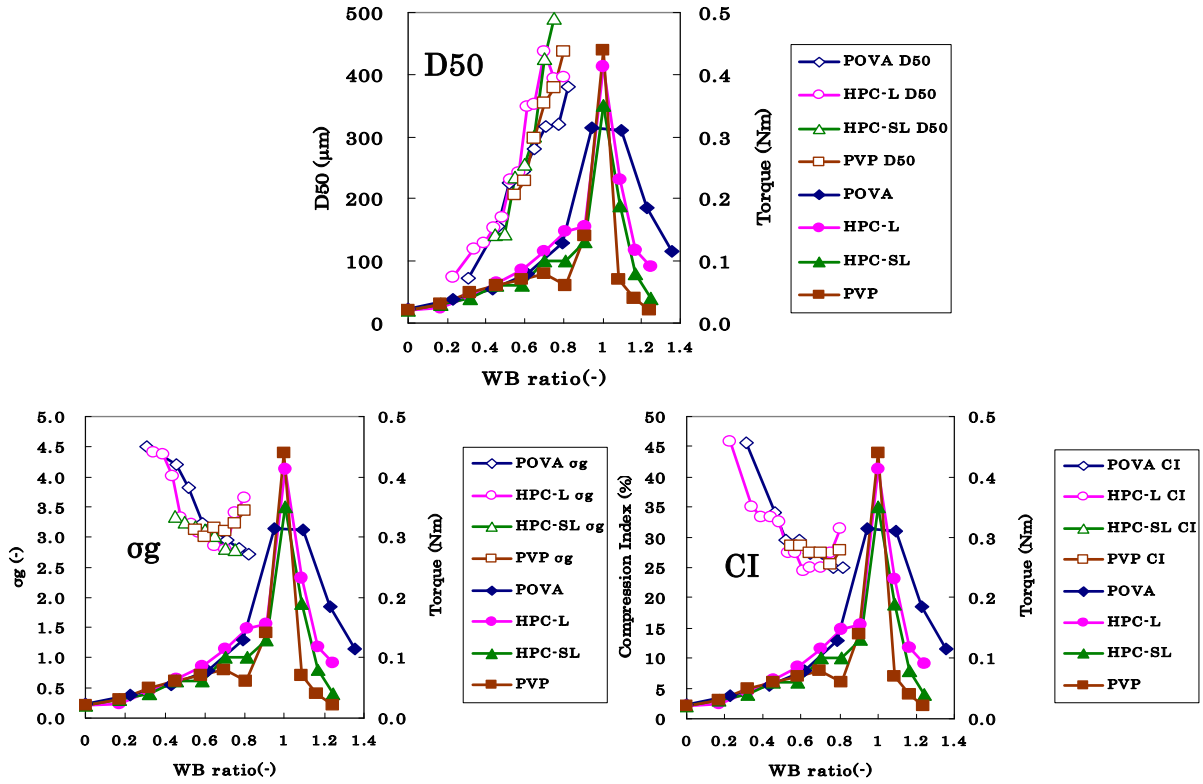


Fig. 8 Plasticity limit (wt%) of granulation with various formula

3-3) Properties of granules

Properties of tabletting granules obtained using placebo formulation with varying WBR of various binders were summarized in Fig.9. Tabletting granules were evaluated by D50, geometric standard deviation(σ g) of particle size distribution denoted the sharpness of particle size distribution and compressibility index of granules (CI) corresponding to flowability of granule mass. From these figures, it was found that favorable i.e., optimized tabletting granules in any cases were obtained at about 0.6 of WBR.

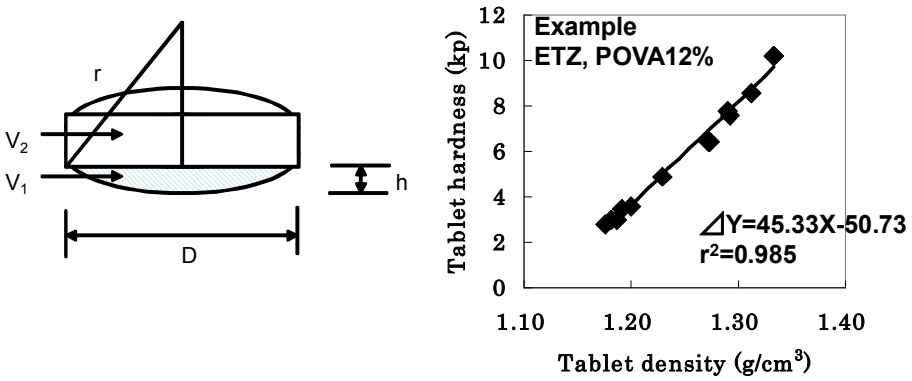


Formulation; placebo (lactose/corn starch=7/3), Binder: 6wt% aqueous solution

Fig. 9 Relationship between granule properties and WBR

3-4) High tablet hardness of POVACOAT

The formability i.e., tablet hardness of optimized tabletting granules at 0.6 of WBR which were obtained with using placebo, ibuprofen, ethenzamide, and acetaminophen were evaluated with varying tabletting pressure. The contents of drug were 50wt% in all drugs containing formulation. In order to clarify the formability of tabletting granules quantitatively, the density of tablet obtained at various tableting pressure was calculated by using an equation shown in Fig.10. The plot of tablet hardness versus density is obtained such as a right figure in Fig.10. Accordingly, formability of tablettig granules can be estimated by the gradient of tablet hardness versus tablet density, quantitatively.



Thickness (h) ; $h=r-((r^2-(D/2)^2)^{1/2}$ 、 Volume (V_1) ; $V_1=\pi(h^2r-h^3/3)$

Volume (V_2) ; V_2 、 Tablet volume (V); $V=2\times V_1+V_2$

Tablet density; Tablet weight (g) / Tablet volume (cm^3)

Fig.10 Calculation of the tablet density and an example of tablet hardness against tablet density

All obtained results of formabilities were summarized in Fig.11. In this figure, POVA MP5% is denoted that micronized particle grade of POVACOAT was used as a powder addition of POVACOAT MP grade in 5%, and kneaded with purified water. It was found that POVACOAT has a higher formability than other polymer in any formulations from the figure. About 0.1 increase of tablet density is corresponded to about 250 kgf of tabletting pressure. The value of 50 of gradient, for example means about 250kgf increase of tabletting pressure makes a 5kp of increase of tablet hardness. In case of acetaminophen (APAP) which is well known as a less formability of API, the capping tendency of tablet was appeared up to 12% of concentration of POVACOAT binder solution similar to other binder. On the other hand, in the case of using a 22.2% solution or powder addition of 5% MP, capping tendency was disappeared. It is furthermore confirmed that using a higher concentration of POVACOAT, for example 22.2% or MP5% is useful to decrease clearly the die friction and sticking tendency.

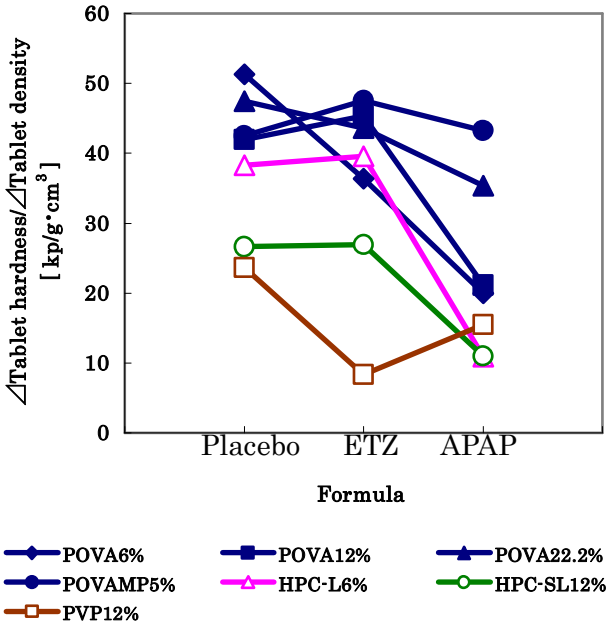


Fig.11 Tablet hardness tendency with using various binder

These results show that using POVACOAT as a binder may be effective to the formulation design and to the prevention of various tabletting troublesome.

3-5) Disintegration of tablet

The disintegration time of tablets obtained at the same density for each formulation were evaluated. The results were summarized in Table 7. Up to 12%, the disintegration time of POVACOAT was comparable to that of other polymer, and using POVACOAT at higher concentration of 22.2% (4% of dry base in formulation) and MP5% make large slightly in the disintegration time.

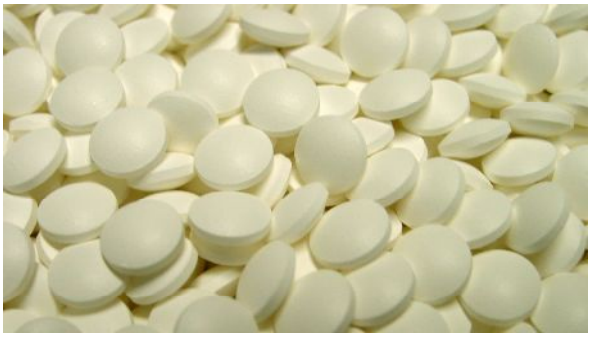
From the above mentioned formability and this disintegration results, it can be concluded that POVACOAT is a granulating binder which has a good balance between the formability i.e., tablet hardness and the disintegration

Table 7 Disintegration time in sec of various formulas

	Placebo	ETZ	APAP
POVA 6%	85	24	38
POVA 12%	236	32	60
POVA 22.2%	182	250	211
POVA MP5%	256	130	80
HPC-L 6%	156	35	52
HPC-SL 12%	182	50	50
PVP 12%	136	20	40

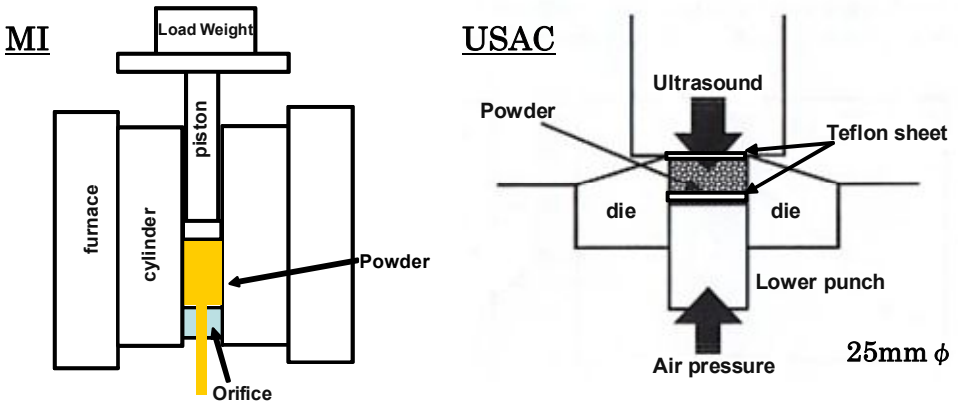
Tablet density (g/cm^3): placebo; 1.35, ETZ; 1.25, APAP; 1.27

JPXV, purified water



4) Solid dispersion matrix

POVACOAT is expected to be applicable as a solid dispersion matrix based on its thermo plasticity. The two different preparing methods for solid dispersion were used, i.e., a melt indexer (MI) and ultrasound assisted compaction (USAC). The schematic diagram of MI and USAC are drawed in Fig.12, respectively.



(Melt Indexer P-101, Toyoseiki Co, Japan) (USTM/L20 20 KHz, I.M.A. S.p.A., Italy)

Fig.12 Schematic diagram of MI and USAC

Melt indexer (MI) was used for the sake of obtaining the preliminary information on POVACOAT solid dispersion by HME. Melt indexer is well used in plastic industry as standard measuring equipment to characterize hot melt plastic flow of polymer. In melt indexer various operating temperature and over load (weight) is available, and moreover MI has a merit in which the sample amount is small in about 3g to 10g. Recently continuous twin-screw extruder is noticed as a mass production machine in the pharmaceutical industry. It is expected to take variable information for applicability of POVACOAT as a HME matrix because of a similarity of operating mechanism of MI to twin-screw extruder.

On the other hand, USAC is noticed as a novel mechanism machine for solid dispersion preparation. Thermoplastic polymer can absorb the ultrasound energy and molds for very short time. Namely, USAC is assumed to be a useful machine for solid dispersion especially by applying to thermo plastic polymer.

MI experiments were carried out as follows; Samples formulated in 1/4/1 of NIF/POVACOAT/glycerin were treated at constant weight of 2160g with various operating temperature. Over 160˚C, sample could be extruded smoothly as a rod-like extrudate. When prepared at operating temperatures above 160℃, NIF exhibited a solubility 3.7 times higher than that of NIF crystals. Fig.13-a) denotes the comparison among POVACOAT with PVA and PVP. All extrudate were obtained by the same operating condition, i.e., 170˚C with a constant weight of 2160g. It is found that POVACOAT has a good ability of solid dispersion formation in comparison with PVA or PVP.

And, USAC experiments were done as follows; Mixtures of nifedipine (NIF), a model drug, of one part and POVACOAT of five parts were molded by ultrasonic irradiation up to 670, 1000 or 1200 J. Over 1000 J, it was found from differential scanning calorimetry and powder X-ray diffractometry that NIF existed in an amorphous state, leading to a high apparent solubility of 35.6 μg/mL, which was 4.5 times higher than that of original NIF crystals (8.0 μg/mL). Fig.13-b) shows a comparison of the results of POVACOAT, HPMC (TC-5) and PVP at the same operating condition (at 1000 joule) The capability of PVA copolymer to make nifedipine amorphous was superior to that of PVP.

These results from MI and USAC suggested that POVACOAT might be efficiently applied to solid dispersion formulation with a high performance.

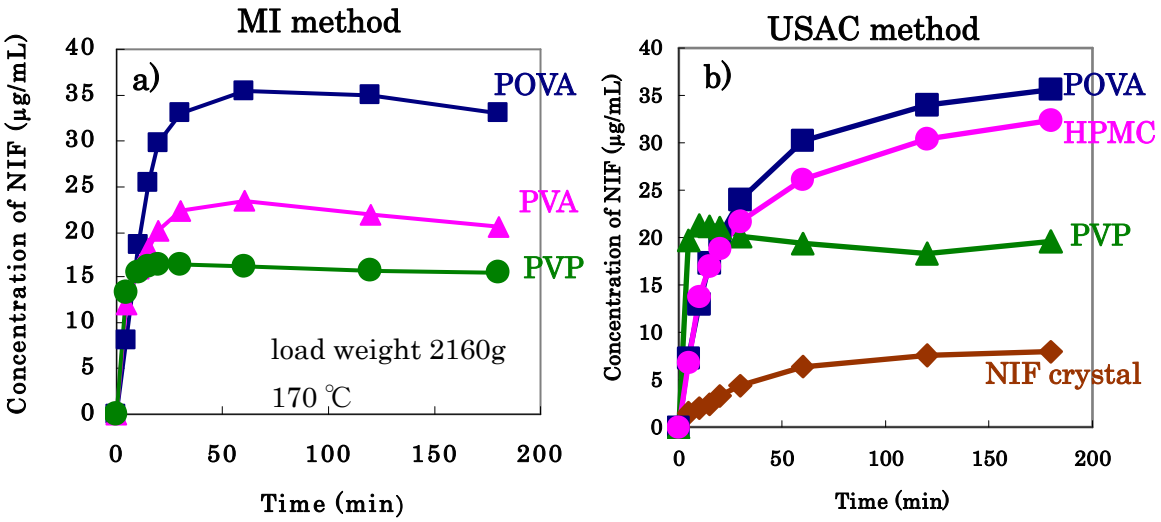


Fig.13 Solubility comparison among polymers with using MI: a) and USAC: b)

< Summery of POVACOAT >

The relationship between the physicochemical properties of POVACOAT and its applicability is shown.

This relationship demonstrates that characteristics such as oxygen barrier function, compactness of the film, stretchable property, oil resistance, thermo plasticity, etc. are utilizable as excipients of various purposes.

Table 8 Correlation among the characteristics of POVACOAT and Application

Characteristics	Hard Capsule	Film Coating	Granulation Binder	Solid Dispersion
Oxygen barrier	○	○		
High elongation		○		
Dense film		○		
Oil resistance	○			
Weak Static electricity	○	○	○	
No Light degradation	○	○	○	○
No Maillard reaction	○	○	○	○
Adhesive on to the surface of granules or Tablets		○	○	
Wetability			○	
Thermoplastic polymer				○

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