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Studies on Protective Coatings. I.[1] The Synthesis and Properties of the Acid Soluble Cellulose Derivatives

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A new type of acid soluble cellulose derivatives, in particular cellulose acetate N,N-dibutylaminohydroxypropyl ether (CABP), have been prepared by the reaction of 1-dialkylamino-2,3-epoxypropanes with the hydroxyl groups in partially hydrolyzed cellulose acetate. The CABP, besides being soluble in a number of common organic solvents, is also soluble in buffer solutions below pH 5.0 but not in neutral aqueous solutions. The compound, therefore, has been found a use in the film coating of tablets which are disintegrated in gastric juice. Water vapor permeability, tensile strength and percent elongation of the free film were tested in comparison with that of cellulose acetate phthalate. The practical coatings on tablets and the disintegration testings were carried out. These results, especially good film forming property, ease of handling and good stability of the film indicated that the CABP was practically useful as a tablet coating agent.

Since cellulose acetate phthalate (CAP), a commercially available and widely accepted coating agent, is soluble in dilute alkali but not in dilute acid, it was considered of interest to prepare a cellulosic coating agent which is soluble in dilute acid and in organic solvent, dut insoluble in water. This paper deals with the preparation of such a cellulose derivative, by reacting the free hydroxyl groups in cellulose acetate,[3] with 1-dibutylamino-2,3-epoxypropane (Chart 1), and the properties of cellulose acetate γ-dibutylamino-β-hydroxypropyl ether (CABP) in the application for pharmaceutical coating.

Owing to the great increase in the number of polymeric materials developed in recent years, much attention[4–6] has been focussed on the application of various basic vinyl polymers to the tablet coatings which will release the medicament in the stomach. However, the coating agent of cellulose derivative containing basic groups has been little exploited.

1) The content of this paper was presented at the 87th Annual Meeting of the Pharmaceutical Society of Japan, Kyoto, April 1967.
2) Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*
3) Hydroxyl groups in cellulose acetate were at least 0.5 per anhydroglucose unit.
4) I. Utsumi, T. Ida, S. Takahashi, and N. Sugimoto, *J. Pharm. Sciences*, **50**, 592 (1961); *ibid.*, **52**, 472 (1963); I. Utsumi, T. Ida, and T. Usuki, *Yakugaku Zasshi*, **78**, 115 (1958); T. Ida, *ibid.*, **78**, 501, 616, 619, 651, 655 (1958); *ibid.*, **79**, 276, 281 (1959).
5) Röhm & Haas Co., Japan. Patent 300627 (1962).
6) Sankyo Co., Japan. Patent 455331 (1961).

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Cellulose acetate diethylaminoacetate (CADA), recently reported by Hiatt and his coworkers,[7] exhibits a number of preferable properties for the coating except for an insufficient stability in esterlinkage of the amino acetate.

For introducing a non hydrolyzable basic radical into cellulose or cellulose derivatives, several reactions have already been tried. The reaction of an aryl sulfonate ester of cellulose with ammonia or an amine,[8] or the reaction of cellulose with an aminoalkyl halide or sulfate[9] gave the derivatives containing basic nitrogens. These approaches, in most cases, were hampered by undesirable side reactions, for instance, formation of quaternary ammonium salts or deacetylation reaction. These side reactions may interfere with solvent solubilities of the products in undesirable manner. Since many uses of cellulose derivatives involve solvents, a considerable emphasis would have to be placed on the solubility in organic solvents.

The reactions between cellulose and 1-dialkylamino-2,3-epoxypropane were studied by G. Montegudet.[10] Application of this method to cellulose acetate having free hydroxyl groups in our hands led to cellulose acetate γ-dialkylamino-β-hydroxyl propyl ether, III (equation 2). These new cellulose derivatives have offered much in fulfilling the requirements of pharmaceutical coating. The use of the materials obtained, especially that of CABP (III, R, R′=C_4H_9-) was extensively investigated.

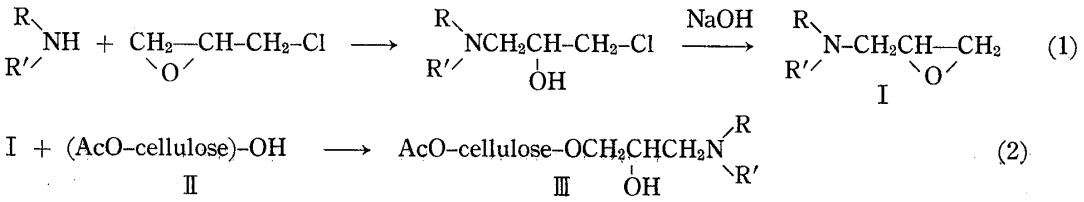
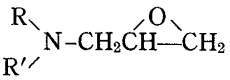
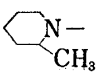


Chart 1

Experimental

Materials——A high acetyl cellulose acetate, acetyl content 39% (2.45 groups per anhydroglucose unit (a.g.u.)) and cellulose acetate phthalate, acetyl content 27.3%, phthalyl content 36.5%, were commer-

Table I. 

R	R′	bp (°C/mm)	
C_2H_5–	C_2H_5–	56—62	(23)
C_3H_7–	C_3H_7–	53.5	(1.5)
C_4H_9–	C_4H_9–	79—81	(2.8)
CH_3–		88.9	(2.5)
CH_3–		92.5	(1.6)
		80.0	(1.3)
		68.5	(7.5)
		58.0	(1.8)

7) G.D. Hiatt, J.W. Mench, and B. Fulkerson, *I.E.C. Product Research & Development*, 3, 295 (1964).
8) *a*) K. Hess and N. Ljubitsch, *Ann.*, **507**, 62 (1933); *b*) V.R. Hardy, U.S. Patent 2136296 (1938); *c*) J.F. Haskins, U.S. Patent 2136299 (1938); *d*) W.O. Kengon, U.S. Patent 2360238 (1944).
9) *a*) C.L. Vaugham, U.S. Patent 2591748 (1948); *b*) Hartmann, U.S. Patent 1777970 (1930); *c*) J.P. Guthyle, *Texitile Research, J.*, **17**, 625 (1947); *d*) R.R. McLaughlin, *Can. J. Chem.*, **33**, 646 (1955).
10) G. Montegudet, *Peintuer, Pigments et Vennis*, **34**, 5, 204 (1958).

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cially available from Daicel Ltd. (Osaka) and Wako Pure Chemical Ind. Ltd. (Osaka),, respectively. The partially saponified cellulose acetate, acetyl content 29.4% (1.54 groups per a.g.u.) was prepared by heating an aqueous solution (water–acetic acid=1:5 by weight) of the high acetyl cellulose acetate in the presence of catalytical amount of sulfuric acid at 60°, followed by the usual reprecipitation procedure. 1–N, N–Dialkylamino–2,3–epoxypropanes were prepared according to the method reported by Gilman, *et al.*[11] Boiling points of these compounds are listed in Table I.

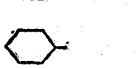
The Typical Preparation of CABP (High Molecular Weight Type)——To a solution of 42.5 g of high acetyl cellulose acetate ([η]=1.80, dioxane at 25°) dissolved in 170 ml of dioxane and 3.8 ml of water, was added 125 g of 1–(N,N–dibutylamino)–2,3–epoxypropane. The mixture was heated at 180° for 9 hr in an autoclave under mechanical stirring. After being diluted of the reaction mixture with 340 ml of dioxane, the resulting solution was poured into 2.7 liter of hexane to precipitate the product, which was filtered, redissolved in acetone (425 ml), and finally reprecipitated into a large amount of water. Washing with distilled water and successive drying at 40° *in vacuo* gave a faint brown fibrous material. Yield, 56.5 g. mp 243° (decomp.). Nitrogen content determined by the micro–Dumas method, 3.1% (dibutylaminohydroxypropyl group 0.89 per a.g.u.). Acetyl content, 18.7% (acetyl groups 1.77 per a.g.u.). Intrinsic viscosity [η]=1.17 in dioxane solution at 25°. Results obtained under the several reaction conditions are shown in Table II.

Table II. Preparation of CABP (High Molecular Weight Type)

Expt. No.	Reaction condition: Cellulose acetate acetyl 39% content (g)	1–Di–butylamino–2,3–epoxypropane (g)	Water (g)	Dioxane (ml)	Temperature (°C)	Time (hr)	Reaction product: Yield (g)	Nitrogen content (%)	Acetyl content (%)	Intrinsic viscosity [η]
1	109	151.5	12.2	600	180	8	133	1.69	22.4	1.46
2	530	1100	53.0	2750	180	8	583	2.06	21.9	1.36
3	530	1120	80	2650	190	9	598	2.65	15.5	1.25
4	530	1200	53.0	2380	190	9	655	2.90	18.0	1.18

The Typical Preparation of CABP (Low Molecular Weight Type)——A mixture of 23.3 g of cellulose acetate (acetyl content 29.4%, [η]=1.40, dioxane at 25°), 180 ml of dioxane, 55.6 g of 1–(N,N–dibutyl-

Table III. Cellulose Acetate γ–Dialkylamino–β–hydroxypropyl Ether (Low Molecular Weight Type)

R	R′	(g)	Reaction condition: Cellulose acetate acetyl content 29.4% (g)	Dioxane (ml)	Reaction temp. (°C)	Reaction time (hr)	Reaction product: Yield (g)	Nitorgen content (%)
C_2H_5-	C_2H_5-	55.0	23.3	180	150	12	28.5	3.47
piperidino—		42.1	23.3	360	150	6	27.2	2.68
piperidino—		49.1	23.3	180	150	6	28.5	2.24
C_3H_7-	C_3H_7-	31.4	23.3	270	150	6	24.8	1.87
C_4H_9-	C_4H_9-	55.6	23.3	180	180	6	32.3	2.12
CH_3-		50.6	23.3	180	150	6	25.8	1.72
CH_3-		44	23.3	110	180	6	29.8	2.39
CH_3-		48	23.3	110	180	6	27.7	2.74
		67.6	23.3	270	150	6	25.6	1.39

11) H. Gilman, C.S. shermen, C.C. Price, R.C. Elderfield, J.T. Maynard, R.H. Reitsema, L. Tolman, S.P. Massie, Jr., F.T. Marshall, L. Goldman, *J. Am. Chem. Soc.*, **68**, 1291 (1949).

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amino)-2,3-epoxypropane was heated for 6 hr at 180° in an autoclave with continuous stirring. After being cooled and diluted with equal volume of dioxane the resinous product was isolated by pouring the mixture into 1.2 liter of hexane. The product was purified by reprecipitation in a similar procedure described above. Yield, 32.3 g. Nitrogen content, 2.12% (dibutylaminohydroxypropyl group 0.47 per a.g.u.). Acetyl content, 20.9% (acetyl groups 1.47 per a.g.u.); $[\eta]=0.915$ (dioxane at 25°). Similarly, the cellulose acetate was esterified with various glycidyl amines (I) and the results are shown in Table III.

Solubility——The solubility tests were run by mixing 0.5 g of cellulose ester with 10 ml of solvent and leaving the mixture at room temperature for 24 hr. The results thus obtained are summarized in Table IV.

Table IV. Solubility of a Typical CABP (HMw-Type)

Solvent	CABP		Solvent	CABP	
	Expt. No. 3[a]	Expt. No. 4[a]		Expt. No. 3	Expt. No. 4
Methanol	+	+	Carbon tetrachloride	−	−
Ethanol	+	−	Diethyl ether	−	−
1-Propanol	−	+	Tetrahydrofuran	+	+
2-Propanol	−	+	Dioxane	+	+
1-Butanol	+	+	Hexane	−	−
sec-Butanol	+	+	Benzene	−	−
Acetone	+	+	Cyclohexane	−	−
Methyl ethyl ketone	+	+	Methyl acetate	+	+
Cyclohexanone	+	+	Ethyl acetate	+	+
Formic acid	+	+	Isopropyl acetate	+	+
Acetic acid	+	+	Pyridine	+	+
Chloroform	+	+	Nitromethane	+	+
Methylene chloride	+	+	Dimethyl formamide	+	+
Ethylene chloride	+	+	Dimethyl sulfoxide	+	+

	nitrogen content	acetyl content	$[\eta]$
a) Expt. 3	2.65%	15.5%	1.25
Expt. 4	2.90	18.0	1.18

solubility code: +=soluble, −=insoluble

Preparation of Cast Films——Preparation of cast films was performed in an air conditioning room at 23° and 50% relative humidity using the apparatus as shown in Fig. 2. Each of 5% solutions of cellulose derivatives was cast as a sheet of 0.5—4 mm wet thickness into a glass cylinder, set on a highly polished glass plate. The flat aluminum plate which was reamed to 25 mm in diameter was placed over the cylinder and a piece of filter paper was then placed on the plate to permit the solvent evaporate slowly. Solvent employed for CAP and CABP were 1) acetone, 2) 1:1 volumetric mixture of acetone-ethanol. The deposited films were dried and kept over 3 days in a vacuum desiccator at 23°.

Water Vapor Permeability of CABP in Comparison with CAP——The water vapor permeabilities of CABP and CAP were determined by the procedure described in JIS[12] Z 0208-53. The thickness of the film was expressed as a mean value measured at 5 different locations with a micrometer caliper. The test was conducted at 40° with 0% humidity inside the cup (maintained by anhydrous calcium chloride) and 89% relative humidity outside. The 89% relative humidity was maintained with a saturated solution of potassium nitrate in a desiccator kept at 40°. The cups were weighed initially and then every 2 hr over a 10 hr time period. The water vapor permeability was calculated using the following formula

$$P=\frac{W\times a}{A\times t\times p}, \qquad (3)$$

where W=increased weight of water, gram; a=film thickness, cm; A=area, cm^2; t=time, sec; p=vapor pressure difference across the film, cmHg.

Tensile Strength and Elongation of CABP and CAP——Films in a thickness range of 0.08—0.2 mm were cut to a uniform size of 10×50 mm using a razor knife. The tesile strength and the elongation were determined using an Instron Tensile Tester (Instron Engineering Corp., Canton, Mass.). The cross-head speed was 5 cm per minute and a distance between the grips was adjusted to 25 mm.

Coating Procedure——In order to evaluate each product (III) for the coating effect on tablets as well as the effect upon disintegration time, selected film coatings were made with (a) placebo tablet, which

12) Japanese Industrial Standard.

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was composed of lactose, starch and magnesium stearate. (b) Vitamin B_1–B_2–C tablet, which contained vitamin C, 30 mg; vitamin B_1 nitrate, 2.0 mg; vitamin B_2, 2.5 mg; lactose, 65.5 mg; starch, 35 mg; talc, 15 mg; total 150 mg. The mean diameter, radius of curvature, thickness and weight of these (a) and (b) tablets were 8 mm, 7.5 mm, 4 mm, and 150 mg, respectively. Coating solutions containing 5% (w/v) of one of cellulose derivatives and 0.5% (w/v) of caster oil as plasticizer in acetone–alcohol (1:1) were applied to the tablets. The application was achieved by spraying the coating solution on the moving bed of tablets in the 15-in. pan,[13] with a hand-operated spray-gun. The coating procedure was based on an intermittent spraying and drying technique; *i.e.*, the tablets were sprayed for a short interval, then tumbled for several second. An air blast was then used to flash off the solvent. When the tablets were apparently dry to insure free tumbling, the air was shut off and the next additional coating was made. The "spraying, tumbling, and drying" cycle then was started again and total sequence of steps continued until the given film weight had been applied. Coated tablets were allowed to dry completely for 12 hr in an oven at 35°.

Disintegration Test——The disintegration test were conducted according to the manner described in U.S. Pharmacopoeia XVII without disk. As shown in Table V, disintegration time of the film on the tablets were determined in the following several media including distilled water, artificial gastric juice and buffered solutions of various acidic pH.

Table V. Disintegration Test of Film Coated Tablets (HMw-Type of CABP)

Sample No.	Coating agent		Coating solution		Coated amount (mg/tablet)[a]	Disintegration time[b]				
	Nitrogen content (%)	Acetyl content (%)	Solvent	Concentration (%)		Distilled water (hr)	Artificial[c] gastric juice (min)	Buffered solution[d] pH 3.0 (min)	pH 4.0 (min)	pH 5.0 (min)
1	1.69	22.4	ethanol–acetone (1:1)	5	10	>3	60	—	—	—
2	2.06	21.9	ethanol–acetone (1:1)	5	10	>3	22	19	45	120
3	2.65	15.5	ethanol–acetone (1:1)	5	10	>3	18	16	27	45
4	2.90	18.0	ethanol–acetone (1:1)	5	10	>3	19	21	21	30

a) vitamin B_1–B_2–C tablet
b) mean time of six tablets each
c) pH 1.2
d) 1/10 M–citric acid –1/5 M–disodium hydrogen phosphate

viscosity——The intrinsic viscosities, $[\eta]$, were obtained by extrapolation of viscosity measurements for several low concentrations of the CABP in dioxane at 25° by the procedure described by Alexander and Mitchell.[14]

Results and Discussion

Screening of Cellulosic Coating Agents

Experiments were conducted to evaluate synthetic cellulosic substances for use as pharmaceutical coatings. As shown in Table III, several basic substituents were introduced into the hydroxyl of partially hydrolyzed cellulose acetates, which are usually produced by acid hydrolysis of the commercially available ester of high acetyl content. Owing to certain unknown depolymerization of the cellulose derivative during the acid hydrolysis and the successive amination reaction, the products (III) obtained revealed somewhat low intrinsic viscosities and were designated the low molecular weight type (LMw-Type). The nature of the substituents on an amino group, R,R′, the molecular weight of III together with the degrees of substitution of acetyl, hydroxyl and the basic group per anhydroglucose unit have a profound influence on the property of III (Tables III, VI and VIII). Preliminary screening tests of the compounds with various R,R′ on the amino group of III revealed that the lower aliphatic or alicyclic amino derivatives, *e.g.* diethylamino–, piperidino–, pipecolino–derivatives

13) The batch size was approximately 1000 tablets, the pan was rotated at 20 rpm.
14) W.J. Alexander and R.L. Mitchell, *Anal. Chem.*, 21, 1497 (1949).

NII-Electronic Library Service

Table VI. Disintegration Test of Film Coated Tablets (LMw-Type of CABP)

Coating material			Coating solution		Coated amount (mg/tablet)[a]	Disintegration time[b]	
Nitrogen content (%)	Acetyl content (%)	Intrinsic viscosity	Solvent	Concentration (%)		Distilled water (hr)	Artificial gastric juice (min)
1.40	22.5	0.903	ethanol–acetone (1:1)	5	5	>3	7
2.12	20.9	0.915	ethanol–acetone (1:1)	5	5	>3	4.5

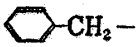
a) placebo tablet b) mean time of six tablets each

Table VII. Disintegration Time of the Tablets stored at Room Temperature for 2.5 Years

Sample No.[a]	Visual inspection of the tablets, stored in the bottle	Disintegration time after 2.5 years				
		Distilled water (hr)	Artificial gastric juice (min)	Buffered solution pH 3.0 (min)	pH 4.0 (min)	pH 5.0 (min)
2	No change	>3	20.5	22.0	75.3	120
3	No change	>3	15.0	15.8	26.5	41.2
4	No change	>3	16.7	20.0	24.7	30.3

a) Each No. of the tablets was taken from the same batch corresponding to the sample number described in Table V.

Table VIII. Disintegration Test of Tablets Coated with Other Derivatives of Cellulose Acetate[a]

Coating material[a]			Coating solution		Coated amount (mg/tablet)[b]	Disintegration time	
Dialkylamino hydroxypropyl ether of cellulose acetate		Nitrogen content (%)	Solvent	Concentration (%)		Distilled water (hr)	Artificial gastric juice (min)
R	R′						
C_2H_5	C_2H_5	1.1	ethanol–acetone (1:1)	5	5	>3	60
C_2H_5	C_2H_5	3.47	ethanol–acetone (1:1)	5	5	0.2	3
C_3H_7	C_3H_7	1.87	ethanol–acetone (1:1)	5	5	>3	8
CH_3		1.72	ethanol–acetone (1:1)	5	5	>3	7
CH_3		2.74	ethanol–acetone (1:1)	5	5	>3	8
		1.39	ethanol–acetone (1:1)	5	5	>3	120

a) low molecular weight type b) placebo tablet

were not suited for the coating agent due to the high solubilities in water. On the other hand, the higher aliphatic or alicyclic amino derivatives, *e.g.* dicyclohexylamino derivative, were inappropriate because the solubility in dilute aqueous acid was too low to expect the rapid disintegration of the coated tablets in the stomach. The intermediate members, such as dibutylamino–, N–methyl–N–benzylamino derivative, were found suitable and CABP was the best in the series at the end of the screening. Although the introduction of a basic

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group did not proceed readily when a commercially available cellulose acetate (acetyl content 39%) was used as starting material, a high molecular weight type of CABP (HMw-Type) was successfully obtained by adding a catalytical amount of water in the reaction system as shown in Table II (equation 2).

D.S. value of each group as well as intrinsic viscosities of the reaction product plotted against the reaction time is shown in Fig. 1. Under the choice of reaction conditions, CABP with various physical properties could be prepared, from which we may choose the composition particularly suited for pharmaceutical coating.

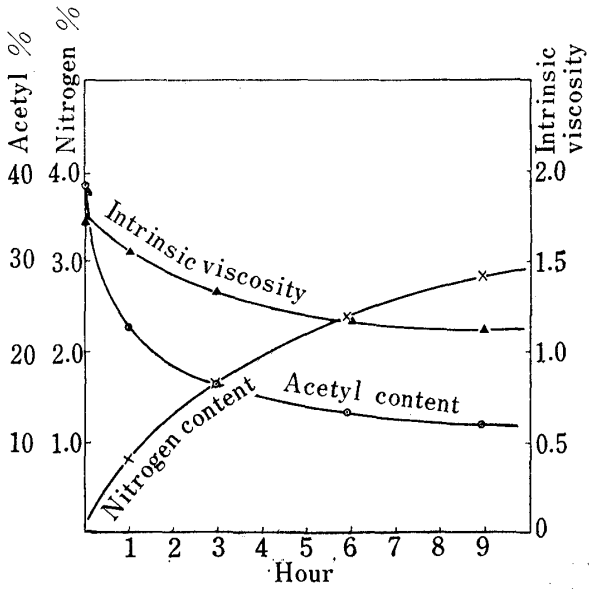

Fig. 1. Relationship between the Composition of CABP and the Reaction Time

initial reaction mixture: cellulose acetate (acetyl content 39%), 42.5 g; dioxane, 200 ml; water, 3.78 ml; 1-N,N-dibutylamino-2,3-epoxypropane, 89.3 g
reaction temperature: 180°
purification procedure: according to the method described in experimental section

Solubility

In general, CABP has a wide range of solubility in organic solvents. Table IV gives a representative listing of solubility characteristics.

Water Vapor Permeability of CABP and CAP

The water vapor permeabilities were determined by the procedure described in the Experimental section. It appears from Fig. 3 that there is no difference between CABP (HMw-Type) and CAP in the value of water vapor permeability constant. The magnitude was in the order of 10^{-10} gm·cm/sec·cm²·cmHg, which indicates that the former would be suited for a film agent comparable to CAP.

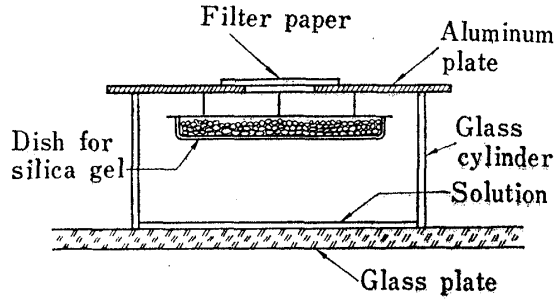

Fig. 2. Apparatus for Film Coating

Tensile Strength and Elongation of CABP and CAP

For practical use in film coating, the per cent elongation and the tensile strength should be high in relative value. Fig. 4 shows that CABP films (HMw-Type) had 3.8 to 5.4 kg/mm² tensile strength with 10 to 45% elongation and exhibited lower tensile strength and a greater elongation as compared with CAP. However, the difference of these mechanical properties between CAP and CABP appears rather insignificant

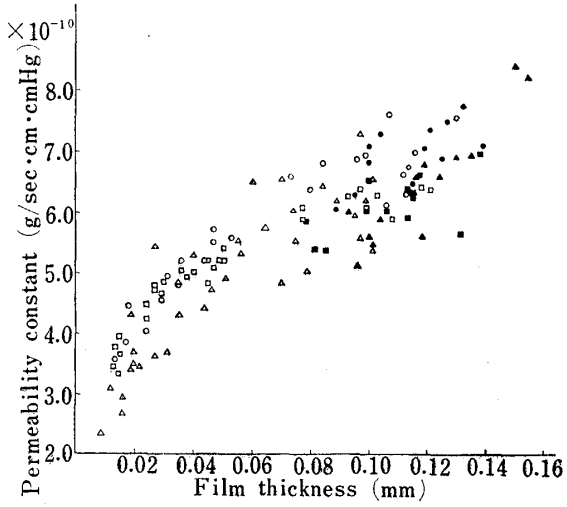

Fig. 3. Variation of Water Vapor Permeability Constant with Film Thickness for CABP and CAP Films

films cast from acetone solution
● CABP[a] ■ CABP[b] ▲ CAP
films cast from acetone-ethanol (5:5, vol.) solution
○ CABP[a] □ CABP[b] △ CAP

a) The film made from CABP, Expt. No. 2 in Table II
b) CABP film from Expt. No. 3 in Table II

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for practical use and both cellulosic materials would have practical applications as suitable film coating agents.

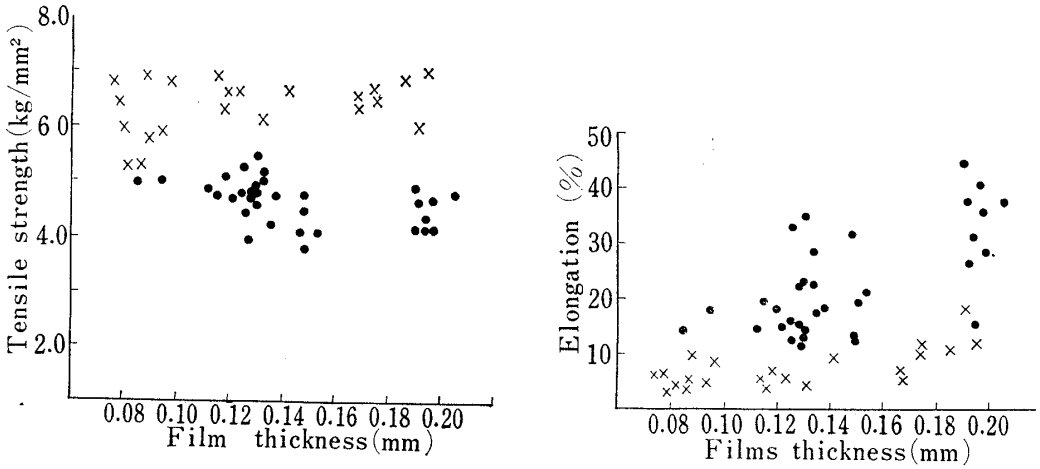

Fig. 4. Tensile Properties of CABP and CAP Films

● CABP (HMW-Type Expt. No. 2) × CAP

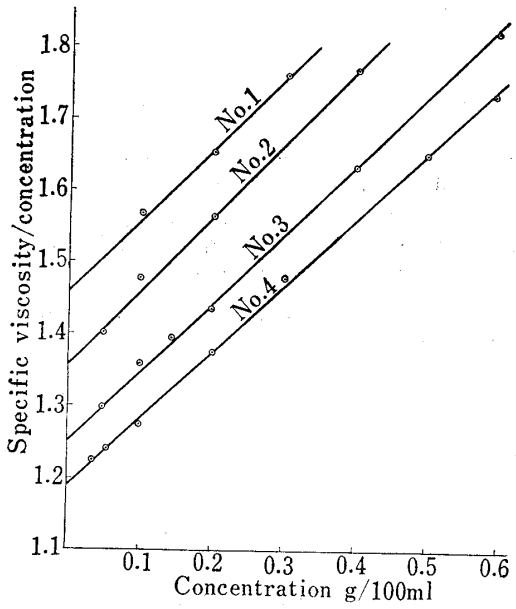

Fig. 5. Viscosity–Concentration Relationship in Dioxane Solution of CABP (HMW-Type) at 25°

Viscosity

Fig. 5 shows a viscosity–concentration relationship of the high molecular weihgt type of CABP.

Evaluation as Tablet Coating

Tablet coatings were conducted as described in the experimental section. Coated tablets were evaluated by visual inspection of film smoothness, edge coverage, luster and uniformity. A 5% coating solution of LMw-Type of CABP produced a coating that was rather brittle whereas the HMw-Type afforded tablets which had transparent, strong and tough film with smooth glossy appearance and showed good disintegration and stability characteristics.

Disintegration Test

The results of disintegration tests are shown in Tables V, VI. For preferable disintegration in artificial gastric juice, the nitrogen content of CABP was observed to be at least 2% in the HMw-Type and 1.4% in the LMw-Type. The solubility of CABP in acidic water appears to decrease with an increase of the molecular weight. The film tablets coated with the HMw-Type which contain 2.65—2.9% of nitrogen disintegrated in a buffer solution of pH 5 within forty-five minutes (Table V).

The data in Table VII were obtained with the coated tablets that had been aged approximately 2.5 years at room temperature. No deterioration of the coating films was observed. The disintegration test *in vivo* was examined in human bodies and the results will be reported elsewhere.

Table VIII shows the result obtained with cellulose acetates having other substituents. Preferable results were obtained with all samples except diethyl- and dicyclohexylamino homologus.

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Toxicity Test

Toxicological data have been obtained for the CABP (HMw–Type, nitrogen content 2.65%). Acute toxicity given orally to mice was $LD_0 > 5$ g/kg. Chronic toxicity studies were conducted by Prof. Ojima and his coworkers, Medical Department of Gifu University(Japan), for 6 months at doses as high as 5 g/kg/day in rats. No visceral changes attributed to the treatment were observed.

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