The cause of the covering of Na-CMC over barium sulfate-particles, carboxyl groups of Na-CMC may take part in the adsorption process, because the addition of MC or PVP has not significant effects on the viscosity and the specific sedimentation volume.

Summary

To investigate the effects of some high polymers on dispersion of barium sulfate particles, rheograms and sedimentation volumes of the suspensions containing sodium carboxymethylcellulose (Na-CMC), methylcellulose (MC) and polyvinylpyrrolidone (PVP) were measured. By the addition of Na-CMC to the suspension, a marked decrease of yield value and apparent viscosity were observed, though MC and PVP increase the apparent viscosity of the suspension. By the addition of 0.2% Na-CMC, the minimum viscosity in Newtonian flow was observed and further addition of Na-CMC increased the apparent viscosity again in pseudoplastic flow. The concentration (0.2% Na-CMC) was consistent well with the one at which the lowest sedimentation volume was attained. MC or PVP did not change the sedimentation volume of the suspension significantly. As the cause of good dispersion of the suspension in the case of Na-CMC, its adsorption on barium sulfate particles was assumed.

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36. Hiroshi Fujiwara, Takatsuka Yashiki, and Tokunosuke Kanzawa :

Rheology of the Pharmaceutical Suspension. IV. Adsorption of Sodium Carboxymethylcellulose on Barium Sulfate Particles in Aqueous Suspension.

(*Research Laboratories, Takeda Chemical Industries, Ltd.*[*1])

In the previous paper,[1] it was observed that the viscosity of barium sulfate suspension decreased by an addition of sodium carboxymethylcellulose (Na-CMC). This phenomenon might be caused by the adsorption of Na-CMC on barium sulfate particles in the suspension. This assumption was ascertained in this paper by determining the amount of adsorbed Na-CMC by the colorimetric method and from the adsorption isotherms obtained it became clear that the adsorption is of Langmuir type.

Experimental

1) Sample

$BaSO_4$: The same product as described previously. Na-CMC : Low, medium and high type Na-CMC (Hercules Co.). This classification is made according to the degree of polimerization of Na-CMC.

2) Determination of the amount of Na-CMC adsorbed.

Several methods were developed by Corner,[2] Houghton,[3] Nile[4] and Szalkowski[5] for

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[*1] Juso, Higashiyodogawa-ku, Osaka (藤原　洋, 矢敷孝司, 神沢得之助).

[1] H. Fujiwara, T. Yashiki, T. Kanzawa : This Bulletin, **11**, 198 (1963).

[2] A. Z. Conner, R. W. Eyler : Anal. Chem., **22**, 1129 (1950).

[3] B. Houghton : J. Soc. Chem. Ind. (London), **60**, 254 (1941).

[4] Nile : Anal. Chem., **21**, 950 (1949); **23**, 1792 (1951).

[5] C. R. Szalkowski, W. G. Marder : J. Am. Pharm. Assoc., **44**, 533 (1955).

the determination of Na-CMC. The methods developed by the former three investigators[2~4] are gravimetric determination of the copper content in a copper salt of CMC. The last method[5] is the colorimetric method which are more applicable than the other, because of the easier procedure. The method employed in this experiment was the modified procedure of this method which will be learned as follows. To 1 ml. of a Na-CMC solution, 14 ml. of 2,7-naphthalenediol reagent was added and the mixture was heated for 75 min. in boiling water. Then it was cooled rapidly in an ice bath and diluted to 20 ml. with H_2O. After 30 min., the extinction of the colored solution was measured with a spectrophotometer (Beckmann B type) at 530 mμ. The exact amount of Na-CMC was determined by comparing the extinction with that of standard Na-CMC solution.

a) Examination of the determination process of Na-CMC

Hydrolysis of Na-CMC and the color reaction between glycolic acid produced and 2,7-naphthalenediol were carried out simultaneously in conc. H_2SO_4. As to the reagent, 100 mg. of 2,7-naphthalenediol was dissolved in 200 ml. of conc. H_2SO_4. In Fig. 1 the relationship between heating period and extinction of the colored solution of 50 γ/ml. Na-CMC are shown. Na-CMC solution must be heated at least for 75 min. This period of time is enough to obtain constant extinction. Relationship between the amount of 2,7-naphthalenediol reagent added and the extinction is shown in Fig. 2. The extinction becomes constant when more than 14 ml. of the reagent is used. The intensity of the color was maintained unchanged for 2 hr. (Table I). In Fig. 3 the calibration curve is shown. Linear relation is obtained between the extinction and the concentration of Na-CMC in solution.

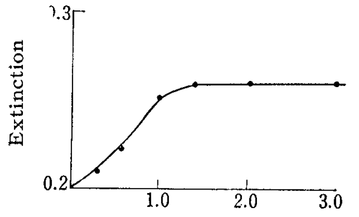

Fig. 1.
Relationship between Reaction Time and Extinction of a Colored Na-CMC solution

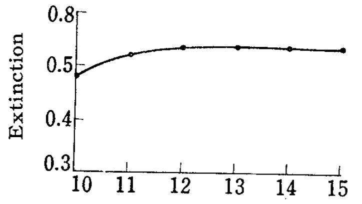

Fig. 2.
Relationship between Amount of 2,7-Naphthalenediol Reagent and Extinction of a Colored Na-CMC Solution

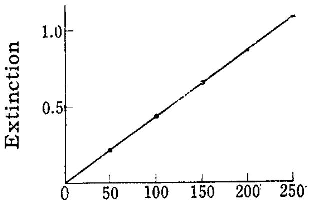

Fig. 3.
Calibration Curve of Na-CMC

Table I. Stability of Colored Na-CMC Solution (30 γ/ml.)

Time elapsed (min.)	Initial	30	60	120
Extinction	0.130	0.130	0.131	0.129
	0.132	0.132	0.132	0.133

b) Measurement of the degree of substitution in Na-CMC molecule

According to Szalkowski, the slope of the calibration curve of Na-CMC is proportional to the number of carboxymethyl groups substituted per glucose residue. Slopes were measured in order to compare the degree of substitution of carboxymethyl group with three types of Na-CMC (low, medium and high type). As shown in Table II, the slopes, or the degree of substitution are coincident well to three types of Na-CMC. The absolute number of carboxymethyl group substituted per glucose residue, however, could not be determined, because Na-CMC of definite degree of substitution was not obtained.

Table II. Relationship between Extinction and Concentration of Na-CMC of Various Types

Type of Na-CMC / Concentration(γ/ml.)	Low	Medium	High
100	0.453	0.450	0.445
80	0.364	0.360	0.357
60	0.273	0.271	0.269
40	0.179	0.180	0.180
20	0.090	0.091	0.089

c) Measurement of the amount of Na-CMC adsorbed

To 2.0～10.0 g. of $BaSO_4$ in a test tube with a glass stopper, 10 ml. of 0.1～0.3% Na-CMC solution was added which was sheared in advance before the viscosity became constant. Then the suspension was shaken for 1 min. vigorously and kept in a thermostat (25±0.1°). Equilibrium of the adsorption of Na-CMC on $BaSO_4$ particles was attained in 5 hr., then the suspension was centrifuged and the amount of Na-CMC in the supernatant solution was determined colorimetrically. The net amount of Na-CMC adsorbed was obtained by subtracting the amount in the equilibrium solution from the amount in the initial solution.

Results and Discussion

1) The Rate of Adsorption

As shown in Fig. 4, the amount of adsorption of Na-CMC increases rapidly at the early stage and equilibrium is attained in 5 hours independently from the concentrations of the suspensions. This period of time is enough to complete the adsorption. During the determination of Na-CMC adsorbed, if any side-reaction except the adsorption would happen between barium sulfate and Na-CMC, the determination is not conducted correctly. A possible side-reaction is the combination of barium ion dissolved with carboxymethyl ion in the solution. However, by the fact that the amount of Na-CMC absorbed became constant after 5 hours, such side-reaction was negligible.

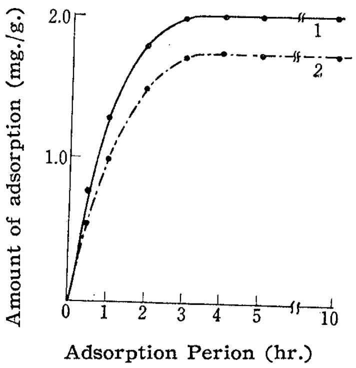

Fig. 4. Relationship between Time and Adsorbed Amount of Na-CMC on Barium Sulfate Particles

1. $BaSO_4$ 10 g. in 0.3% Na-CMC Solution 10 ml.
2. $BaSO_4$ 2 g. in 0.1% Na-CMC Solution 10 ml.

2) Adsorption Isotherm of Na-CMC (High Type)

As shown in the adsorption isotherm (Fig. 5), the amount of adsorption increases rapidly at a low concentration and saturated adsorption is observed at a higher concentration of Na-CMC in equilibrium solution (over 0.1%). The amount of Na-CMC in saturated adsorption is 1.80 mg./g. of barium sulfate. This amount coincides well with the concentration at which Newtonian flow is observable.

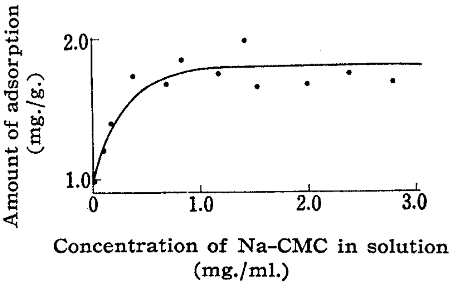

Fig. 5. Adsorption Isotherm of Na-CMC (High-Type) on Barium Sulfate Suspension at 25°C

3) Adsorption Isotherms of other Types of Na-CMC

The adsorption isotherms of low, medium, and high types of Na-CMC are of the same type as shown in Figs. 5, 6, and 7. The amount of Na-CMC in saturated adsorption is 1.75 mg./g. in medium type and 1.90 mg./g. in low type and they are also coincident virtually with 1.80 mg./g. in high type of Na-CMC. This fact is explained by assuming that Na-CMC molecule is not adsorbed perpendicularly to the plane of the adsorbent, but is adsorbed laterally.

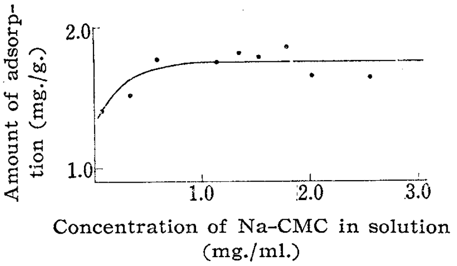

Fig. 6. Adsorption Isotherm of Na-CMC (Medium-Type) on Barium Sulfate Suspension at 25°C

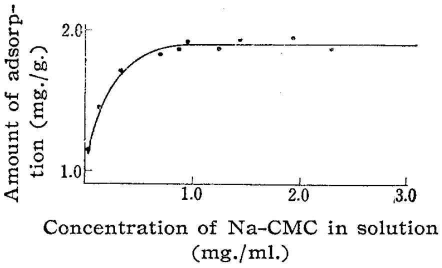

Fig. 7. Adsorption Isotherm of Na-CMC (Low-Type) on Barium Sulfate Suspension at 25°C

From the observation that the flow properties did not differ significantly when either methylcellulose or polyvinylpyrrolidone was added to the suspension as reported in the previous paper,[1] it may be assumed that the adsorption is caused by the interaction between carboxymethyl groups of Na-CMC and active sites of barium sulfate particles. Further, by analyzing the amounts of Na-CMC in saturated adsorption statistically, mean value, variance and standard deviation were obtained. Table III shows the values calculated from the plateau part of the isotherms (Figs. 5, 6, and 7). Variance in high or medium type is significant in comparison with variance in low type. This result may be explained as follows. The longer the chain of Na-CMC, the more various configuration would be taken in adsorption, and as the amount of adsorption depends on the configuration, the variance would be larger in the cases of high and medium types of Na-CMC.

TABLE III. Mean Value, Variance and Standard Deviation of Amount of Saturated Adsorption

Type of Na-CMC	d.f	Mean value (mg./g.)	Variance	Standard deviation
Low	8	1.90	0.0083	0.092
Medium	8	1.75	0.0877	0.296
High	9	1.80	0.2333	0.483

4) Effect of an Addition of Sodium Chloride on the Adsorption

It is well known that in a very dilute Na-CMC solution (below 0.2% or 0.3%) steep rise of reduced viscosity of the solution is observed as the concentration of Na-CMC decreases, but when strong electrolytes is added to it, linear relation between reduced viscosity and the concectration of Na-CMC is obtained. This phenomenon is observable in most ionizing high polymers and is explaned by Hirai and others[6,7] as follows. At such low concentrations, owing to the intramolecular repulsion among dissociated segments, a molecule takes more expanded form, which causes the abnormal high reduced viscosity. If some strong electrolyte is added to the solution, however, the dissociation of a high polymer is suppressed and such expansion does not occur. Then, change of the amount of adsorption was presumable when sodium chloride was added to the barium sulfate suspension in Na-CMC solution. Adsorption isotherm was measured when 0.23% sodium chloride was added to the Na-CMC solution (high type). At the addition of such concentration of sodium chloride, linear correlation was observed between reduced viscosity and the concentration of Na-CMC. The same type of adsorption isotherm was shown in Fig. 8. The amount of Na-CMC in saturated adsorption

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[6] N. Hirai, H. Nishimura: Nippon Kagaku Zasshi, **75**, 248 (1954).
[7] N. Hirai: Kōbunshi Kagaku, **14**, 256 (1957).

(2.55 mg./g. of barium sulfate) is rather larger than that observed without sodium chloride. This increase may be due to the adsorption of Na-CMC in more contracted form by an addition of sodium chloride.

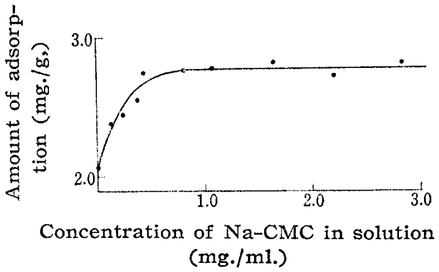

Fig. 8. Adsorption Isotherm of Na-CMC on Barium Sulfate Suspension containing NaCl at 25°C

5) Application of Langmuir Equation

Three adsorption isotherms (Figs. 5, 6, and 7) suggest that these adsorption may be in accordance with the Langmuir adsorption. The Langmuir equation (1) was applied to the adsorption.

$$c/x/m=1/a\cdot b+c/a \qquad (1)$$

Where, c is the concentration of Na-CMC solution in equilibrium, x/m the amount of Na-CMC adsorbed per g. of barium sulfate, a is the amount of Na-CMC in saturated adsorption and b is constant relating to the strength of the adsorption.

As shown in Fig. 9, linear relationship is observed between x/m and c, and it is clear, therefore, that the adsorption is in accordance with the Langmuir adsorption well. The straight line obtained from Langmuir plot passes origin, which means that the first term of the right hand in the equation (1) is zero and b must be infinitive as a takes a finite value. Then, it may be reasonable to conclude that the adsorption-force of Na-CMC on barium sulfate particles is very strong, and may be due to the coulombic interaction between carboxymethyl ion and localized positive charge of barium sulfate particles.

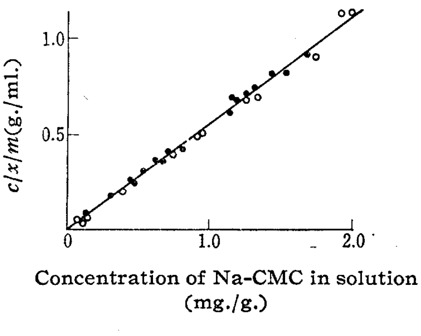

Fig. 9. Application of Langmuir Equation to the Isothermal Adsorption of Various Types of Na-CMC on Barium Sulfate Suspension

- • High Type
- ⊙ Medium Type
- ○ Low Type

Summary

To ascertain the assumption that sodium carboxymethyl cellulose (Na-CMC) is adsorbed on barium sulfate particles, the amount of Na-CMC adsorbed was determined by the colorimetric method. The shapes of the adsorption isotherms showed a steep rise and then a flat top where the amount of Na-CMC adsorbed did not change appreciably with increasing the concentration of Na-CMC solution. From the adsorption isotherms, it became clear that the Langmuir equation was in accordance well with the adsorption. The amount of Na-CMC adsorbed in saturated adsorption was 1.90 mg., 1.75 mg., and 1.80 mg. per g. of barium sulfate in low, medium and high types of Na-CMC

respectively and the fairly consistency of the amounts in spite of the difference of the molecular weight suggests that Na-CMC is attached laterally to the plane of the particles in the adsorption. These amounts are also consistent well with the concentration at which the minimum viscosity in Newtonian flow and lowest sedimentation volume were observed as described in the previous paper. Moreover, by the addition of sodium chloride to the Na-CMC solution, the amount of Na-CMC adsorbed increased to 2.55 mg./g. of barium sulfate. This is ascribed to the contraction of Na-CMC molecule, which is caused by the suppression of dissociation in the presence of sodium chloride.

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37. **Michihiro Yamada, Kazuaki Iizuka, Shigenobu Okuda, Toshinobu Asai und Kyosuke Tsuda :** Untersuchungen auf dem Gebiet der mikrobiologischen Umsetzung. XVIII.[1] Umwandlung von Alkaloiden in der Morphin-Reihe durch *Trametes sanguinea.* (3).

(*Institut für angewandte Mikrobiologie der Universität Tokio*[*1])

Wie in den vorherigen Mitteilungen dieser Reihe[1,2] berichtet wurde, läßt sich die Carbonylgruppe an C_6 in Codeinon mit *Trametes sanguinea* zur Hydroxylgruppe reduzieren. Die Autoren versuchten diesmal die Reduktion der Carbonylgruppe an C_6 bei einem 14β-substituierten Codeinon zu erreichen, wobei ihnen interessierte, ob sich diese Verbindungen mit *T.sanguinea* an der Carbonylgruppe reduzierend angreifen lassen, und ob diese enzymatische Reaktion stereospezifisch verläuft. Als Substanzen dienten 14β-Acetoxycodeinon[3] und 14β-Bromcodeinon.[4]

Die Fermentationen wurden bei 30° unter aeroben Bedingungen in Schüttelkulturen durchgeführt; als Nährlösung wurde eine wäßrige Lösung von Glukose (1%), Pepton (0.2%), Rindfleischextrakt (0.1%), Hefeextrakt (0.1%) und Corn-steep-liquor (0.3%) verwendet.[*2] Die Umsetzung wurde vorläufig papierchromatographisch verfolgt und dann in präparativem Maßstab ausgeführt.

Die Umsetzung von 14β-Acetoxycodeinon (I) verlief sehr befriedigend. Das Umsetzungsprodukt ließ sich mit einer Ausbeute von ca. 70% gewinnen, und es bestand aus einer einzigen Substanz; im Papierchromatogramm konnte nur ein Fleck von Rf 0.30[*3] erhalten werden. Das gereinigte Produkt vom Schmp. 157~157.5° erwies sich nach Schmelzpunkt, Misch-Schmelzpunkt, Papierchromatogramm und Infrarot-Spektrum als identisch mit 14β-Hydroxycodein (II).[5] Bei dieser Umsetzung findet also außer der Reduktion der Carbonylgruppe noch eine Reaktion, d. h. der Ersatz der Acetoxylgruppe

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[*1] Yayoicho, Bunkioku, Tokio (山田道弘, 飯塚和明, 奥田重信, 朝井勇宣, 津田恭介).

[*2] Diese Lösung eignete sich zur Reduktion der Carbonylgruppe des Codeinons. Siehe auch Fußnote 1 und 2.

[*3] Nach der Methode von Büchi durchgeführt : Bull. on Narcot., 1960, April-June, 25.

1) K. Iizuka, M. Yamada, J. Suzuki, I. Seki, K. Aida, S. Okuda, T. Asai, K. Tsuda : Dieses Bulletin, **10**, 67 (1962).

2) M. Yamada, K. Iizuka, S. Okuda, T. Asai, K. Tsuda : *Ibid.*, **10**, 981 (1962).

3) R.E. Lutz, L. Small : J. Org. Chem., **4**, 220 (1939).

4) H. Conroy : J. Am. Chem. Soc., **77**, 5960 (1955).

5) A.C. Currie, J. Gillon, G.T. Newhold, F.S. Spring : J. Chem. Soc., **1960**, 773.