Rheology of Microcrystalline Cellulose-Carboxymethylcellulose Gels

By W. DOUGLAS WALKLING* and RALPH F. SHANGRAW

Rheological evaluations of MCC-CMC gels were employed to delineate their properties. It was concluded that the thixotropic nature of MCC-CMC gels depended upon the adsorption of the soluble CMC on the MCC. A certain degree of shear was required to unsheave the microcrystals. However, excessive shear reduced the degree of structuring. MCC-CMC in concentrations of 2.0 percent or higher produced thixotropic gels. CMC was found to be superior to HPMC as a linking polymer. At the concentration studied, alcohol and various glycols increased the viscosity of MCC-CMC gels independently of the viscosity of the adjuvant compound. Formulations containing acetaminophen and calamine in MCC-CMC systems were also evaluated.

ONE APPROACH to the preparation of pharmaceutically acceptable suspension systems involves the utilization of agents which possess different rheological properties. Samyn (1), in particular, has suggested that a combination of plastic and pseudoplastic suspending agents offers unique pharmaceutical advantages. The plastic agent would prevent low stress sedimentation or leakage while the pseudoplastic agent would assist high stress flow. Samyn investigated magnesium aluminum silicate-sodium carboxymethylcellulose systems. Simple pseudoplastic systems were found to settle with time while plain clay suspensions entrapped air and presented pouring problems. Combinations of the order of 0.6% magnesium aluminum silicate and 1.3% sodium carboxymethylcellulose were found to give superior results.

The insoluble magnesium aluminum silicate clay utilized by Samyn in his work actually imparted both plasticity and thixotropy to his suspension systems. Recently, a new suspending agent has become available which resembles this overall system but is unique in that the plasticity or thixotropy is imparted by microcrystals of organic cellulose. This agent, microcrystalline cellulose-carboxymethylcellulose[1] (MCC-CMC) is a specially prepared blend of 92 parts of microcrystalline cellulose and 8 parts of sodium carboxymethylcellulose with not more than 4% moisture at the time of manufacture. As a powder, 97% of the material will pass through a No. 325 mesh sieve, and, as a dispersion, the ultimate particle size varies around 0.15 μ (2). It is insoluble in water and organic solvents, but it disperses to form colloidal sols and opaque gels. Hydration is rapid and changes little if any on aging.

In order to postulate a mechanism for the structured formation on MCC gels, Hermans (3) forwarded the concept of primary reaction sites which lead to strong aggregation without branching and weaker secondary sites which cause branching. Consequently, when shear is introduced into a dispersion of MCC, linear aggregates formed by the primary reaction sites orient to the streamlines of flow and thus permit the secondary reaction sites to form branched networks as the microcrystals align themselves in a tighter, more parallel pattern. The thixotropy and high yield values observed in MCC-CMC gels are claimed to be due to the adsorption of the dissolved sodium CMC polymers onto the cellulose microcrystals (4). Consequently, the greater the number of surfaces for adsorption, the more extensive the structured network, the greater the thixotropy and yield value of the gel will be.

The purpose of this investigation is to explore and further define the rheological properties of MCC-CMC gels.

EXPERIMENTAL

All experiments were conducted using a Haake Rotovisco rotating viscometer (Polyscience Corp., Evanston, Ill., 60602). The MV system for medium viscosities and the type 50 and type 500 measuring heads were employed. A MV-1 plastic rotor with a 0.6-cm. height and a 2.004-cm. radius was employed along with a 2.10-cm. radius cup. These variables permitted a rate of shear range of 8.46 to 1,370 sec.$^{-1}$ and a shearing stress range of 7 to 3,540 dynes cm.$^{-2}$. The operating temperature for all experiments was 28°.

Preserved water containing 0.15% methylparaben and 0.02% propylparaben was employed in all formulations. All gels were prepared in terms of percent weight to weight.

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[1] Marketed as Avicel RC by American Viscose Div., FMC Corp., Marcus Hook, Pa.

Process Variables—Two percent gels of MCC-CMC were prepared in 500-g. quantities with various types of laboratory apparatus in order to determine which method produced the best gel.

Method I—Ten grams of MCC-CMC was added to 240 g. of water in a 1-qt. Waring blender, model PB-5A. The mixture was sheared at the highest speed for 9 min. Another 250 g. of water was added, and shearing was continued for another 11 min. The dispersion was then passed twice through an Eppenbach colloid mill, 1725 r.p.m. drive, adjusted to the "2" setting.

Method II—Ten grams of MCC-CMC was dispersed over a 5-min. period into 490 g. of water placed in a 1,000-ml. beaker. Dispersion was facilitated by means of a Talboy's mixer, model 101, operated at the "30" setting. The propeller was inserted midway into the liquid. After the powder was dispersed, mixing was continued for 30 min.

Method III—Same as Method II except that the final product was passed twice through the Eppenbach colloid mill.

Method IV—Same as Method III except that mixing was continued for 60 min.

Previous experience with these systems showed that at concentrations of 2% or less, 1 hr. of aging permitted the formation of an essentially static system. For higher concentrations, 24 hr. of aging was found to be sufficient.

Method III was selected as the method to be used in all other experiments. The basis for this selection will be discussed later.

Concentration—Gels of 1.0, 2.0, and 4.0% MCC-CMC were prepared. All preparations were aged 24 hr. prior to rheological evaluation.

Carboxymethylcellulose—Gels of 1.0, 2.0, and 4.0% of an 80/20 and a 50/50 blend of MCC-CMC and CMC were prepared. Solutions of the CMC, 300–500 cps. grade,[2] were added to fully dispersed gels of MCC-CMC. The combinations were blended by a Lightnin mixer, model V-7, adjusted to the "10" setting. After blending, each mixture was passed twice through the Eppenbach colloid mill.

Hydroxypropyl Methylcellulose—Using hydroxypropyl methylcellulose (HPMC), 3500–5600 cps. grade,[3] 80/20 blends of MCC-CMC and HPMC were prepared in the same manner as the MCC-CMC/CMC blends.

Alcohol and Glycols—The effects of common suspension adjuncts on 2.0% MCC-CMC gels were investigated. Blends containing 20.0% alcohol, glycerin, PEG 200, and propylene glycol were prepared. Solutions of the hydrophilic compounds were added to fully dispersed gels. The mixtures blended readily and additional shear through a colloid mill was not required.

Medicinal Agents—Samples of acetaminophen[4] and calamine were incorporated into gels so that the final concentration of the medicinal agent was 10.0% and that of the gel was 2.0%. A control suspension and a suspension utilizing 2.0% magnesium aluminum silicate[5] (MAS) as the suspending medium were also studied. All samples were aged 30 days at an ambient temperature of approximately 26°.

Structural Breakdown with Time—In order to evaluate thixotropy in greater detail, a time-dependence study was designed. Samples of gels containing 4.0% gelling agent with or without 10.0% acetaminophen or calamine were placed in the viscometer cup and allowed to remain there for 30 min. before commencing shear. The use of 4.0% agent permitted a more critical evaluation of the parameter. After the dwell period, the sample was sheared for 10 min. at one rate of shear. The sample was then replaced and the process repeated on another sample at another rate of shear. All samples were aged for 24 hr. except the MAS preparation which was aged for 30 days.

RESULTS AND DISCUSSION

MCC-CMC may be the first of a new class of pharmaceutical suspending agents. It is a blend of organic celluloses which develop gels having a high degree of thixotropy. The thixotropic structure rebuilds rapidly, and unlike other thixotropic pharmaceutical vehicles, its rheological properties do not change further upon aging. In addition, the effects of added substances on suspension properties are immediately reflected.

Most of the properties of MCC-CMC are detectable through simple laboratory techniques such as agitation, bottle inversion, and macroscopic observation. Though quantitative data are presented to define and measure these properties, a discussion of these data is desirable in terms of the mechanism of MCC-CMC gel structure formation, how this structure is altered by various substances, and how it can be applied to pharmaceutical formulations.

A unique and perplexing problem which was encountered in the preparation of MCC-CMC gels was their combined dependence upon and sensitivity to shear. A certain amount of shear was required to establish the maximum gel structure. This is believed to be due to the unsheaving of microcrystals which exposes more cellulose surface on which the CMC may be adsorbed. Microscopic examination of a weakly thixotropic dispersion and a highly

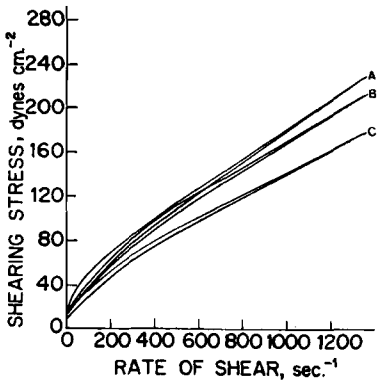

Fig. 1—Influence of processing variables on the rheology of 2% MCC-CMC gels. Key: A, Method III; B, Method IV; C, Method I. Method II would appear between A and B.

[2] Marketed as CMC-7MP by Hercules Powder Co., Inc., Wilmington, Del.
[3] Marketed as Methocel 90 HG Premium, 4000 cps., by Dow Chemical Co., Midland, Mich.
[4] Marketed as acetaminophen, NF, Micropowder, by S. B. Penick and Co., N. Y.
[5] Marketed as Veegum HV by R. T. Vanderbilt Co., Inc., Norwalk, Conn.

thixotropic gel made from the same concentration of MCC-CMC revealed that the weakly thixotropic dispersion contained many large bundles of microcrystals of cellulose while the other preparation contained only faintly visible microcrystals. As more cellulose surface became available, the possibility of adsorbing interconnecting or bridging soluble polymers increased. These interconnecting soluble polymers caused a structured, thixotropic network to be formed. The degree of thixotropy can be increased by either unsheaving the microcrystals or by increasing the length of the soluble polymer chains. Increasing the concentration of the soluble polymer was effective up to about a 20% increase. About that point, the pseudoplastic nature of the soluble polymer started to overwhelm the system.

As can be seen in Fig. 1, passing suspensions through the Eppenbach colloid mill subsequent to mixing increased the gel structure. Apparently, a certain percentage of the microcrystals was not unsheaved by mixing alone. With the colloid mill, a reasonably reproducible shear was obtained since all of the material was exposed to the same degree of shear by passage through a predetermined orifice. Such was not the case with the Waring blender or the simple mixer.

However, it can also be seen that too much shear resulted in a partially destructured system. The existence of such a phenomenon in MCC-CMC gels has been verified by Raynor (5). An explanation for this is disclosed in the work of Healy and LaMer (6). These investigators adsorbed polyacrylamide on calcium phosphate. The addition of a small amount of polymer formed unit flocs. The addition of more polymer caused bridging between the unit flocs to produce a three-dimensional macrofloc with a high degree of structure. Bridging occurred even though only half of the calculated adsorption sites on the calcium phosphate particles were occupied. At this point, agitation of the system destroyed the three-dimensional macrofloc as energy was imparted to the system. This destruction was not thixotropic breakdown as structure did not rebuild itself spontaneously. Further bridging could not occur now until all of the adsorption sites had reacted with the polymer and energy was subsequently reduced. Thus, shear had produced a system with a permanently lowered consistency.

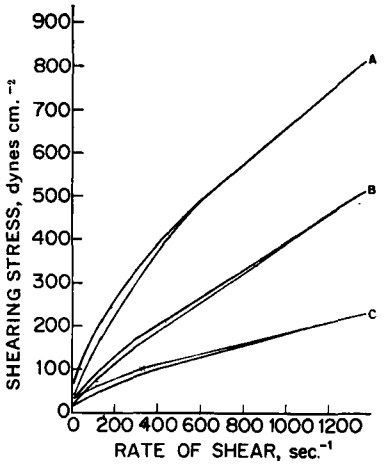

Fig. 3—Effect of CMC on the rheology of MCC-CMC gels. 2% combined polymer concn. employed. Key: A, MCC-CMC/CMC 50/50; B, MCC-CMC/CMC 80/20; C, MCC-CMC only.

Though the MCC-CMC gels are not the same as the calcium phosphate-polyacrylamide system, both systems involve the adsorption of a soluble polymer onto an insoluble particle, and both systems show evidence that, above a certain concentration of the respective materials, a structured network exists. Excessive shear during the unsheaving of the microcrystals may have decreased the structuring potential of this system by causing the soluble polymer to entwine around individual or groups of microcrystals and thus decrease the chance of intercrystal adsorption. The soluble cellulose polymer then serves as a protective colloid which inhibits rather than promotes interparticle structuring.

The thixotropy, yield values, and apparent viscosities of MCC-CMC gels increased with increasing concentration as evidenced in Fig. 2. At the 4.0% level, the rheogram exhibited definite evidence of a "foot." A "foot" occurs when the structure is

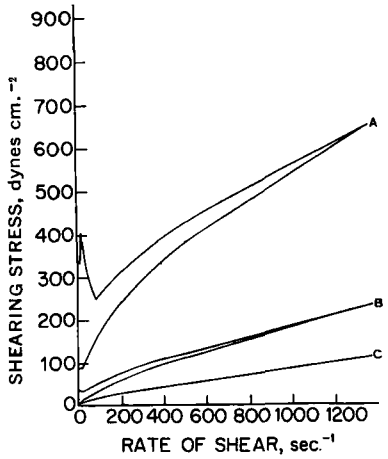

Fig. 2—Effect of concentration on the rheology of MCC-CMC gels. Key: A, 4%; B, 2%; C, 1%.

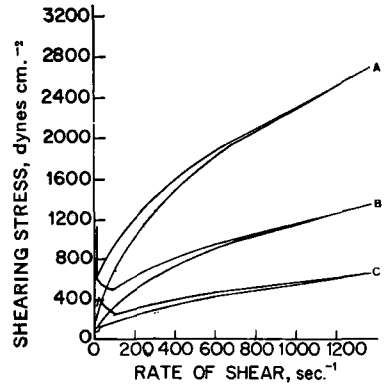

Fig. 4—Effect of CMC on the rheology of MCC-CMC gels. 4% combined polymer concn. employed. Key: A, MCC-CMC/CMC 50/50; B, MCC-CMC/CMC 80/20; C, MCC-CMC only.

TABLE I—EFFECT OF CONCENTRATION ON THE RHEOLOGY OF MCC-CMC/CMC AND MCC-CMC/HPMC 80/20 GELS

Rate of Shear, sec.$^{-1}$	Shearing Stress (dynes cm.$^{-2}$) CMC, 1%	CMC, 2%	CMC, 4%	HPMC, 1%	HPMC, 2%	HPMC, 4%
8.46	7	28	779	14	112	957
16.9	11	37	620	11	89	886
25.4	12	46	549	12	93	779
50.7	18	65	514	18	105	709
76.1	23	79	496	21	116	638
152	33	112	567	32	147	655
228	47	140	620	39	172	691
457	77	219	815	65	247	886
685	103	301	992	88	309	1,050
1,370	170	514	1,350	149	496	1,400
685	102	275	957	86	295	1,030
457	74	209	744	63	228	850
228	40	126	496	39	147	620
152	32	96	407	28	119	514
76.1	21	61	283	19	81	390
50.7	18	47	248	18	65	337
25.4	12	30	177	12	46	266
16.9	9	23	159	11	37	230
8.46	7	16	124	7	26	177

broken with a force far greater than that necessary to establish thixotropic equilibrium; hence, a very rapid and real decrease in the yield value takes place before equilibrium is attained (7). Naturally, the force imparted to the structure varies from instrument to instrument, and it is, therefore, more dependent upon the test conditions than anything else. Though difficult to reproduce quantitatively, the foot is real and must be given consideration.

Figures 3 and 4 show the effects of CMC on MCC-CMC gels. Table I shows that HPMC, 4,000 cps. grade, and CMC, medium viscosity (300–500 cps.) grade, had nearly identical influences upon MCC-CMC gels even though pure solutions of the former were much more viscous than the latter. The rheological similarity of the combined gel products was the result of the greater interaction between the MCC and the CMC as opposed to the interaction between the MCC and the nonionic HPMC.

The effects of pharmaceutical adjuvants can be seen in Table II. It is curious to note that alcohol, glycerin, PEG 200, and propylene glycol, materials of quite different viscosities, elicited the same effects on 2.0% MCC-CMC gels when employed in 20% concentrations. Apparently, the criteria for the structure of these mixtures were not the viscosity of the adjuvants themselves, but the presence of hydroxyl groups. Thixotropy and yield values went unchanged upon the addition to the adjuvants though apparent viscosity increased. At higher concentration levels, the effects of alcohols began to vary and the viscosity of the individual agent became a factor. Syrup and sorbitol solution had the same general effects as the other agents, *i.e.*, no effect on thixotropy and yield values but a marked increase in the apparent viscosity.

The rheological effects of the various suspending agents in combination with 10.0% acetaminophen

TABLE II—EFFECT OF 20% ALCOHOL AND GLYCOLS ON THE RHEOLOGY OF 2% MCC-CMC GELS

Rate of Shear, sec.$^{-1}$	Shearing Stress (dynes cm.$^{-2}$) Alcohol	Glycerin	PEG 200	Propylene Glycol
8.46	25	26	28	25
16.9	32	35	39	33
25.4	39	40	42	40
50.7	56	56	58	56
76.1	67	67	68	68
152	95	96	98	98
228	116	116	119	121
457	179	179	182	186
685	228	228	230	235
1,370	351	351	351	389
685	219	214	221	224
457	161	161	167	168
228	98	96	100	102
152	75	75	77	77
76.1	51	49	51	51
50.7	39	39	40	40
25.4	26	25	28	26
16.9	21	21	23	21
8.46	16	16	16	16

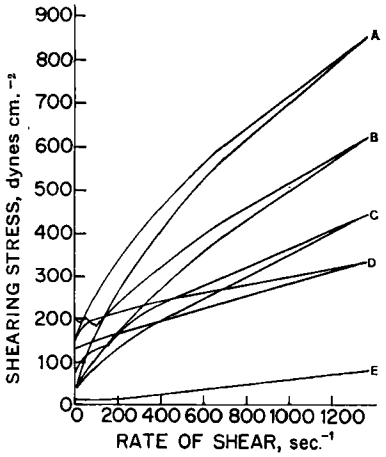

Fig. 5—Rheology of 10% acetaminophen suspensions. Key: A, MCC-CMC/CMC 80/20; B, MCC-CMC/HPMC 80/20; C, MCC-CMC; D, MAS; E, no susp. agent. 2% susp. agent and 30 days aging for all preparations.

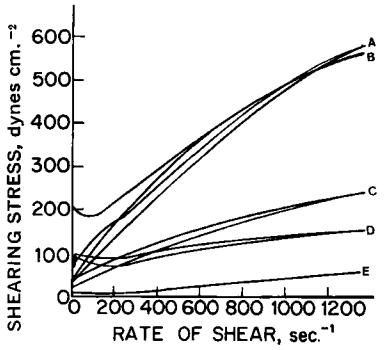

Fig. 6—Rheology of 10% calamine suspensions. Key: A, MCC-CMC/CMC 80/20; B, MCC-CMC/HPMC 80/20; C, MCC-CMC; D, MAS; E, no susp. agent. 2% susp. agent and 30 days aging for all preparations.

are presented in Fig. 5. In every case, thixotropy, yield value, and apparent viscosity were markedly increased. Although consistency effects in complete suspension formulations almost always exceed the sum of the effects of the individual components, acetaminophen systems exhibited exaggerated increases which could only result from drug-suspending agent interactions at a structural level. This can no doubt be attributed to the fine particle size of the acetaminophen and the presence of polar groups which provided additional adsorption sites for the soluble cellulose polymers allowing acetaminophen to play an active role in the structuring of the system. However, the fact that the consistency increases were particularly marked in the systems containing the higher quantities of CMC indicates that the anionic nature of that soluble polymer was particularly important in this interaction.

Calamine (Fig. 6) gave an excellent suspension with MCC-CMC. No unusual synergistic consistency increases were noted.

The effects of shear and time of shearing stress are shown in Tables III–V. In all cases, more structural breakdown occurred during the first minute than at any other time. Though not indicated by the data, the breakdown was most rapid during the first few seconds. When compared with MAS, MCC-CMC exhibited approximately the same yield stress at the lowest rate of shear. The clay exhibited a small foot at the lower rates of shear while the MCC-CMC produced a much larger foot. Breakdown was far more rapid and more complete in the MAS systems. Practical experience with suspensions containing 4.0% MCC-CMC showed that the amount of breakdown achieved with only moderate

Table III—Effect of Rate of Shear Per Unit Time on the Shearing Stress of MCC-CMC Gels

Rate of Shear, Sec.⁻¹	Shearing Stress (dynes cm.⁻²) 0 min.	1 min.	3 min.	10 min.
		4% MCC-CMC		
8.46	349	119	93	70
16.9	319	116	95	79
25.4	461	119	103	91
50.7	585	147	132	117
76.1	602	161	147	133
152	478	193	177	163
228	602	235	214	200
457	602	372	337	274
685	638	425	407	372
1,370	921	638	585	531
		4% MCC-CMC/CMC 80/20		
8.46	531	200	154	119
16.9	638	189	151	126
25.4	744	217	177	147
50.7	762	256	216	191
76.1	868	295	260	240
152	921	425	390	372
228	957	496	478	452
457	1,134	744	726	691
685	1,240	921	903	868
1,370	1,559	1,311	1,258	1,205

TABLE IV—EFFECT OF RATE OF SHEAR PER UNIT TIME ON THE SHEARING STRESS OF 4% MAS GEL (AGED 30 DAYS)

Rate of Shear, sec.$^{-1}$	Shearing Stress (dynes cm.$^{-2}$) 0 min.	1 min.	3 min.	10 min.
8.46	337	182	175	175
16.9	337	160	151	151
25.4	390	156	147	144
50.7	354	142	128	123
76.1	390	144	132	126
152	425	158	149	142
228	425	170	161	156
457	443	205	196	193
685	531	231	219	216
1,370	815	319	270	265

shaking was sufficient to allow rapid flow through a narrow-neck bottle. However, since a high degree of structure was still present after shaking, better retardation of sedimentation would have resulted during the static period immediately following the shear. The addition of CMC to the MCC-CMC gel increased the shearing stresses at all rates of shear and reduced thixotropy due to its inherent psuedoplastic nature.

Ten percent acetaminophen greatly increased the shearing stresses at all rates of shear. But what was most interesting was the enormous thixotropic breakdown which was produced during the first minute and probably during the first few seconds of shearing. In other words, the acetaminophen interacted with the polymers to produce a highly structured gel. However, since the molecular size was so small in relation to the polymers and since most of the drug was present as insoluble particles, the structural breakdown was very rapid. In a practical sense, a suspension of 10.0% acetaminophen in a 4.0% gel of MCC-CMC would remain suspended at rest, but would break down easily to a freely flowing liquid.

The experiences with 10.0% calamine in 4.0% MCC-CMC were similar to those just described for acetaminophen though the structure of the system was not as great.

Consequently, it appeared that a 4.0% concentration of MCC-CMC functioned effectively as a suspending agent for both a weakly soluble, acidic organic compound and an insoluble inorganic oxide.

CONCLUSIONS

Careful control over the preparation of MCC-CMC gels is important. A certain amount of shear is necessary to completely develop gel structure; however, excessive shear can interfere with the structuring of the system.

Gels are thixotropic when concentrations of 2% or higher of MCC-CMC are employed.

Gel structure is brought about by the adsorption of soluble cellulose polymers onto insoluble cellulose microcrystals. This system is unique in the realm of pharmaceutical suspending agents.

The anionic nature of CMC makes it superior to HPMC as a linking polymer.

TABLE V—EFFECT OF RATE OF SHEAR PER UNIT TIME ON THE SHEARING STRESS OF 4% MCC-CMC GELS

Rate of Shear, sec.$^{-1}$	Shearing Stress (dynes cm.$^{-2}$) 0 min.	1 min.	3 min.	10 min.
	10% Acetaminophen			
8.46	461	372	312	249
16.9	744	390	256	184
25.4	921	407	244	202
50.7	957	281	235	212
76.1	1,098	284	249	231
152	1,275	390	354	316
228	1,240	390	372	326
457	1,258	585	567	549
685	1,169	620	602	602
1,370	1,169	833	797	762
	10% Calamine			
8.46	461	283	210	130
16.9	602	249	154	130
25.4	762	207	156	137
50.7	921	200	172	154
76.1	939	214	191	179
152	939	261	242	224
228	886	425	390	354
457	1,205	496	452	425
685	1,346	531	478	461
1,370	1,134	726	673	638

At the concentration studied, alcohol and various glycols increase the viscosity of the gels to the same extent.

Compounds capable of interacting with CMC increase the viscosity of the gels.

Acetaminophen demonstrates extensive interaction with MCC-CMC.

REFERENCES

(1) Samyn, J. C., *J. Pharm. Sci.*, **50**, 517(1961).
(2) *Avicel RC Microcryst. Cellulose and Its Use in Pharm. Susp.*, Am. Viscose Div., FMC Corp., Marcus Hook, Pa., p. 1.
(3) Hermans, J., Jr., *J. Appl. Polymer Sci.*, **9**, 1973(1965).
(4) *Avicel RC Microcryst. Cellulose and Its Use in Pharm. Susp.*, Am. Viscose Div., FMC Corp., Marcus Hook, Pa., p. 2.
(5) Raynor, G. E., personal communication (July 6, 1966).
(6) Healy, T. W., and LaMer, V. K., *J. Colloid Sci.*, **19** 323(1964).
(7) Green, H., "Industrial Rheology and Rheological Structures," Wiley, New York, N. Y., 1949, p. 69.

Keyphrases

Microcrystalline cellulose (MCC)-carboxymethylcellulose (CMC)-gels
Rheology—MCC-CMC gels
Suspending adjuvants, effect—gels
Shear rate, stress range, effect—gels

Absorption, Metabolism, and Excretion of the Ephedrines in Man II

Pharmacokinetics

By G. R. WILKINSON* and A. H. BECKETT

The kinetics of absorption, metabolism, and excretion of (−)-norephedrine, (−)-ephedrine, and (−)-methylephedrine, after oral administration in aqueous solution, have been elucidated using analog computer analysis of urinary excretion data from three male subjects under constant acidic urine control. The kinetics of formation and elimination of norephedrine and ephedrine when present as metabolites have also been determined. The single body compartment mathematical models were based upon a catenary chain with parallel branch systems and all rate constants were assumed to be first order. Excellent agreement was obtained between the theoretical computer curves and the experimental excretion data for both unchanged drug and metabolite(s).

THE DEVELOPMENT of mathematical models to describe the absorption and fate of a drug and its metabolite(s) in the body, and the value of such models in the design of dosage forms and regimens has been treated by numerous authors including Teorell (1), Dominguez (2), Dost (3), Nelson (4), Wagner (5), Krüger-Thiemer (6) and references therein. For maximum exploitation of these techniques drug plasma levels are preferable, however, the distribution characteristics of many drugs, especially basic drugs (7), are such that this information is not readily available. In these cases it is possible to use urinary excretion data providing caution is taken in the interpretation of the results (8, 9).

In view of the long and extensive use of the ephedrines[1] it is surprising that relatively little is known about the kinetics of their absorption and elimination in man. The only published information concerns (−)-norephedrine, where the mean elimination half-life was reported to be 3.9 hr. (10). Recent publications (11, 12) have indicated that the relative metabolism and urinary excretion of the ephedrines are dependent upon the urinary pH and in certain circumstances the volume also. The validity of urinary excretion kinetics is based upon the assumption that the excretion rate reflects the plasma concentration of the drug. With drugs exhibiting non-

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[1] The term ephedrines will be used to describe collectively the levo isomers of norephedrine, ephedrine, and methylephedrine.