

# Investigation of a Cellulosic Polymer-Polyhydroxyl Polymer Interacted Polyelectrolyte System I

## Rheology and Suspension Characteristics

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The rheological investigation of a series of aqueous cellulose polymer (carboxymethylhydroxyethylcellulose)-polyhydroxyl compound (polyethylene glycol) systems showed large increases in  $\eta'$  (indicator of viscosity) as determined using the power law equation ( $\eta' = F^N/G$ ). These increases were most predominant when the lower molecular weight polyethylene glycols were evaluated with CMHEC. A computer program was written using Fortran for the IBM 7090/1401 computer system for solution of the power law equation and determination of regression coefficients. Certain of these CMHEC-polyethylene glycol systems were used as vehicles in preparing 10 per cent suspensions containing either zinc oxide or sulfamerazine calcomites. Superior suspension stability was noted for both insoluble drugs in the interacted systems with little or no phase separation and no caking occurring in a 120-day observation period.

SUSPENSIONS represent an important class of preparations. The suspending agent used in such systems should be tolerant to and effectively stabilize both positively and negatively surface charged insoluble drugs. Pharmaceutical suspending agents commonly used are either clays (silicates of aluminum, magnesium, and other trace components) or polymers (viscosity imparting fractions of natural gums, or celluloses, alginates, etc.). The polymeric suspending agents are usually polyelectrolytes. Polyelectrolytes have been defined as substances which, on dissolving in water or other ionizing solvents, dissociate to give polyions, multiply charged ions together with an equivalent amount of ions of small charge opposite in sign. Polyelectrolytes yielding appreciable amounts of polyions of high charge are necessarily macromolecular. High polymeric polyelectrolytes thus constitute a special class of polyelectrolytes. They may be a polyacid, polybase, or polyampholyte (1). The various polymeric polyelectrolyte suspending agents do not contain an ionic balance of positive and negative charged centers; this accounts for the fact that they do not equally suspend various insoluble materials that differ in degree or nature of surface charge.

Various methods have been described in the literature as approaches to the stabilization of suspension systems involving rheological control or flocculation. One method involved coating of the insoluble particles to nullify the surface charges, after which they are flocculated under controlled conditions and suspended in a non-

ionic vehicle (2-5). The reduction of the insoluble particle to a very fine particle size and the adjustment of the vehicle density (6, 7) is another. The use of polymeric agents to alter the surface charges on particles is well illustrated by the numerous applications of polyelectrolytes. It was theorized that the use of combinations of these polymeric agents may produce suspensions of improved stability resulting from the polyelectrolyte nature of the polymeric suspension vehicle and the enhancement of rheological properties (increased viscosity primarily) resulting from polymer interactions.

Polyelectrolytes have been widely used as flocculating agents for numerous purposes, including soil conditioning (8-11), treatment of slimes and clay dispersions (12-15), and water treatment (16-18). Various mechanisms have been described to attempt to explain how these polymer materials function in the flocculation process. Ion exchange is mentioned as one mechanism (10); other authors stress the importance of certain polymer groups to the phenomena (19).

Virtually every possible rheological approach to the preparation of suspension vehicles which produce permanent suspensions has been reported. The use of pseudoplastic-plastic systems has been advocated (20), as have pseudoplastic-thixotropic systems (21) and plastic high yield value systems (22). Another non-physical method of altering the rheology of polymeric systems is accomplished with the addition of glycerol to these systems (23-26).

The use of the power law equation permits the most precise rheological evaluation of pseudoplastic systems (27). The relationship  $\eta' = F^N/G$  as proposed (28, 29) has been used to eval-

Received June 3, 1963, from the School of Pharmacy, Purdue University, Lafayette, Ind.

Accepted for publication August 10, 1964.

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Presented to the Scientific Section, A.P.H.A., Miami Beach meeting, May 1963.

uate pseudoplastic systems where it has been found applicable (30, 31). It has been stated (32) that it is an empirical fact that many observational results in many diversified fields of science, if plotted on a log-log scale, give straight lines. The power law equation is an analytical expression of this empirical fact. An excellent review (27) of the various types of flow behavior together with the power law equation and some of its limitations has been described.

The primary purpose of this study was to investigate the application of certain pharmacologically inert polyelectrolyte nonionic polymer combinations as suspension vehicles and stabilizers. The major objective was the selection of a combination of a polyelectrolyte and a nonionic polymer that would provide enhanced rheological properties (primarily viscosity increases) and a simultaneous ionic-nonionic balance which would stabilize insoluble drugs in suspension. The nonionic component of such a system might be presumed to act in two ways in such an interacted system in promoting suspension stability: (a) by producing altered rheological properties and (b) by coating the particles to produce a flocculated or stable nonflocculated system.

## EXPERIMENTAL

**Materials.**—A preliminary screening of certain cellulose polymers and polyhydroxyl compounds resulted in the selection of CMHEC combinations with polyethylene glycols for further study on the basis of altered rheological properties shown by these systems. Carboxymethylhydroxyethylcellulose, in two viscosity grades, CMHEC 43L and 37L<sup>1</sup> and polyethylene glycols<sup>2</sup> in a molecular weight range of 200 to 9000, were evaluated. Samples of each of the CMHEC polymers were dried *in vacuo* at 65° and 20 mm. Hg until constant weight was achieved (16 to 20 hours), and a correction factor was then applied to the subsequent weighings of the cellulose polymers based on the predetermined volatiles content. Zinc oxide U.S.P. was used as the positive surface-charged particle and had a particle size range less than 5  $\mu$ . Sulfamerazine calcomites (American Cyanamid Co., Fine Chemicals Division, Pearl River, N. Y.) was used as the negatively surface-charged particle and had a particle size range between 2 and 10  $\mu$ . Particle sizes less than 36  $\mu$  in the final suspension product were necessary to permit evaluation by the cone and plate viscometer using the truncated cone.

**Equipment.**—A Lightnin V-7 mixer (Mixing Equipment Co., Inc., Rochester, N. Y.) was used at low speed in the preparation of the dispersions of the polymer and suspension systems. The polymer and suspension systems after dispersion were passed once through the Manton Gaulin 2B colloid mill (model 2B-RE, Manton Gaulin Co., Everett, Mass.)

for uniformity. The Ferranti Shirley cone and plate viscometer (Ferranti Ltd., Manchester, England. In U.S.A., Ferranti Electric Inc., Electronics Division, Plainview, Long Island, N. Y.) with an automatic cycling arrangement was used in the rheological phase of the study (33, 34). A Precision Scientific circulating water bath model 6600 thermostated at  $25 \pm 1^\circ$  was used in conjunction with the cone and plate viscometer. The regular large and medium cones of the viscometer were used for the polymeric combination evaluation, and the large truncated cone was used for the suspension systems.

**Procedures.**—The various polymeric combinations of CMHEC 43L, 37L, and polyethylene glycol, together with the  $N$  and  $\eta'$  values determined from the rheogram data using the power law equation, are shown in Tables II to V. The particular suspension systems evaluated rheologically, together with the  $N$ ,  $\eta'$ , and thixotropic areas in square centimeters<sup>3</sup> are shown in Tables VI to IX. The suspension systems were prepared in sufficient quantities to have an adequate sample for rheological evaluation and for the settling rate study where indicated. The suspension systems were all prepared in a standardized manner to avoid changes which may occur due to the method of preparation. Settling rate tubes<sup>4</sup> were prepared of each of the suspension samples; each contained approximately 100 ml. and were stored in special racks for observation. The suspensions and the polymer combinations were in all instances evaluated rheologically after 24 hours and within 48 hours after preparation.

The cone and plate viscometer with automatic cycling was operated to obtain a complete rheogram tracing in 60 seconds with a top r.p.m. of 72 with the Mosely XYT recorder at the settings,  $x = 10$  v. and  $y = 100$  v. The maximum shear rates obtained with the various cones used were: large cone, 1303.8 sec.<sup>-1</sup>; medium cone, 1291.0 sec.<sup>-1</sup>; and the large particle cone, 320.7 sec.<sup>-1</sup>. The maximum shear stress possible with each particular cone was: large cone, 10,935 dynes/cm.<sup>2</sup>; medium cone, 55,935 dynes/cm.<sup>2</sup>; and the large particle cone, 12,290 dynes/cm.<sup>2</sup>.

The initial calibrations of the viscometer were made using NBS standard oils. The power law equation was initially applied to the polymer combination rheograms and found applicable. The important fact to remember when using the power law equation is that the log-log plot of shear rate *versus* shear stress must be linear and that  $N$  (slope) is greater than 1 for pseudoplastics. The power law equation used (26, 27) is given in the form

$$F^N = \eta' G \quad (\text{Eq. 1})$$

$$N \log F = \log \eta' + \log G \quad (\text{Eq. 2})$$

$$\log G = N \log F + \log 1/\eta' \quad (\text{Eq. 3})$$

where  $F$  = shearing stress (reading 500),  $G$  = shearing rate (r.p.m.),  $1/\eta' = y$  intercept,  $\eta'$  = indicator of viscosity, and  $N$  = index of non-Newtonian behavior (33).

Equation 3 was used to calculate  $N$  and  $\eta'$  using the computer program. A general scheme was used throughout the evaluation procedure in the selection

<sup>1</sup> Hercules Powder Co., Wilmington, Del.

<sup>2</sup> Carbowax 200, 300, 400, 600, products of Union Carbide Chemicals Co., New York, N. Y. Polyglycol 1000, 4000, 6000, 9000, products of Dow Chemical Co., Midland, Mich.

<sup>3</sup> Keuffel & Esser 4242 compensating polar planimeter.

<sup>4</sup> Flint glass tubes with 18-mm. i.d., and 20-mm. o.d. cut to sufficient length to contain readily 100 ml. using No. 2 or No. 3 stoppers.

TABLE I.—EVALUATION OF CMHEC POLYMERS WITH THE POWER LAW EQUATION DOWN-CURVE DATA

Concn. Pol., %	CMHEC 43L		Concn. Pol., %	CMHEC 37L	
	<i>N</i>	$\eta'$		<i>N</i>	$\eta'$
1	1.2903	110.45	1	0.9639	5.62
2	1.3046	170.78	2	1.1804	50.32
3	1.3407	200.52	3	1.4215	468.08
4	1.4757	1872.36	4	1.4451	5897.67
5	1.4833	857.39	5	1.4162	2516.52

of the data points from the rheograms. These data points were selected from the up curve, down curve, or both. The set of data points consisted of five r.p.m. graph division values and the corresponding five (reading 500) graph division values of the rheogram taken at approximately equal arithmetic intervals. These respective values were converted to absolute values for computation by the Fortran program with the application of certain constants. To facilitate the computational procedures, a Fortran program was written for the power law equation as applied to the IBM 7090/1401 computer system.

The data and the source program were punched on IBM cards using the IBM 026 punch-card machine and verified using the IBM 407 accounting machine with appropriate panel board.<sup>5</sup>

The program made provision for the expression of the following data from each rheogram, and for computation of the parameters indicated:

- run (ranged from 001 to 999),
- the five  $x$  values (reading 500), the five  $y$  values (r.p.m.),
- $\eta'$ ,  $b$ ,  $a$ ,  $r$ ,  $r^2$

where  $\eta = \eta'$  (indicator of viscosity),  $b = \text{slope } (N, \text{ index of non-Newtonian behavior})$ ,  $a = 1/\eta$ , and  $r = \text{linear correlation coefficient}$ .

The importance of  $r$  cannot be overemphasized in the computational procedure since it gives a ready indication of the linearity of the log shear rate–log shear stress plot and therefore the validity of the relationship for a particular set of data.

## RESULTS AND DISCUSSION

**Rheological Aspects of the Polymeric Combinations.**—The polymeric combination systems evaluated together with the  $N$  and  $\eta'$  values for the systems are given in Tables II to V. Table I gives the control polymer data. Generally, there was some slight lot-to-lot variation within the CMHEC type used; however, the same basic trends were observed.

The influence of the molecular weight of the polyethylene glycol used with the CMHEC 43L or 37L has a considerable effect on the extent to which  $\eta'$  will change. Both the up curve and down curve of the polymer systems were evaluated by the power law relationship, but only the down curve data are shown in Tables II–V. The  $\eta'$  and  $N$  values shown in Tables II–V each represent an average of the computations of three rheograms. The calculated  $r$  (linear correlation coefficient) ranged from 0.995 to 0.998, an indication of good adherence of the rheogram data to the basic conditions of the power law equation.

Considerable variation in  $\eta'$  was noted, even though there was apparent replication from visual

observation of the rheograms, an indication that small changes in  $N$  produce exaggerated changes in  $\eta'$ , as would be expected.

Tables II and III show the  $N$  and  $\eta'$  values obtained from the rheological data for the down curve for the CMHEC 43L–polyethylene glycol 200–9000 systems. Some of the data points are shown in Table III for  $N$  less than 1, an indication of deviation from pseudoplasticity; more likely, the systems were too fluid to be evaluated accurately by the cone and plate viscometer under the present conditions of instrumentation.

Tables IV and V show the  $N$  and  $\eta'$  values obtained from the rheological data for the down curve of the CMHEC 37L–polyethylene glycol 200–600 systems. The  $N$  and  $\eta'$  values for these systems are considerably smaller than they were for the CMHEC 43L and corresponding polyethylene glycol systems. For this reason, after the screening procedure was almost completed, further screening of CMHEC 37L with higher molecular weight polyethylene glycols was not considered necessary.

In a study of the tabulated rheological data, particularly the  $\eta'$  values and to a lesser degree the  $N$  values, specific advantages of the CMHEC–polyethylene glycol systems may be noted. When Table I is compared to Tables II or IV, it is observed that the CMHEC concentrations required in the CMHEC–polyethylene glycol systems are smaller than in the CMHEC system to achieve similar  $\eta'$  values. Therefore, it is possible to use lower concentrations of CMHEC with the low molecular weight polyethylene glycols to achieve higher  $\eta'$  values than are possible with the CMHEC systems alone.

### Rheological Aspect of the Suspension Systems.—

The suspension evaluation was conducted with CMHEC 43L and polyethylene glycol systems which had shown maximum interaction based on  $\eta'$  from the studies shown in Tables II and IV. The systems evaluated contained either 10% zinc oxide or 10% sulfamerazine calcomites. It is important to consider the effect of particle charge on suspension characteristics, as indicated in this study. The assumption is made in these systems that the polyethylene glycol preferentially coats the respective insoluble particles and at the same time interacts with the CMHEC polymer.

After an initial testing of the power law equation using both the up curve and down curve data points of the rheograms, only the down curve obeyed the basic conditions of the power law equation. The down curve was used in all the computations for the suspension systems listed in Tables VI to IX. Considerable thixotropy was noted, particularly with the 4% concentration of the cellulose polymer present. The thixotropy increased with an increase in concentration of polyethylene glycol and polyethylene glycol molecular weight grade used. The hysteresis loops were measured with a compensating

<sup>5</sup> See original thesis (35) for further details of the computer aspect of the study.



TABLE IV.—CMHEC 37L DOWN CURVE  $\eta'$  VALUES USING PEG 200-600

% PEG-% Pol.	$\bar{M} = 200$	$\bar{M} = 300$	$\bar{M} = 400$	$\bar{M} = 600$
5-1	22.3	0.8	56.0	10.4
5-2	47.5	9.3	2.7	23.3
5-3	24.1	30.8	356.2	6.8
5-4	257.5	25.8	955.1	183.6
5-5	345.2	385.9	3,101.4	293.9
10-1	7.4	0.2	1.7	7.3
10-2	147.8	7.6	1.8	6.0
10-3	725.7	95.6	3.5	34.9
10-4	338.8	234.0	405.7	2,526.2
10-5	4,017.7	373.6	2,097.7	2,029.4
20-1	4.1	0.6	1.3	10.6
20-2	38.5	57.9	11.2	14.6
20-3	255.9	53.8	125.0	71.9
20-4	1,345.6	414.4	5,823.7	1,637.6
20-5	1,289.4	3,353.8	14,409.5	20,950.9
30-1	9.4	2.9	28.9	1.0
30-2	101.0	129.7	62.1	16.5
30-3	61.3	81.1	5,291.7	54.9
30-4	6,231.2	2,029.8	4,428.8	10,477.9
30-5	54,225.8	20,427.7	79,022.7	13,145.0

TABLE V.—CMHEC 37L DOWN CURVE " $N$ " VALUES USING PEG 200-600

% PEG-% Pol.	$\bar{M} = 200$	$\bar{M} = 300$	$\bar{M} = 400$	$\bar{M} = 600$
5-1	1.1055	0.7533	1.2044	1.0881
5-2	1.1744	1.0007	0.8743	1.1033
5-3	1.1093	1.1404	1.4011	0.9724
5-4	1.3689	1.1003	1.3448	1.3300
5-5	1.3969	1.3981	1.3858	1.1658
10-1	0.8765	0.6830	0.8227	0.9851
10-2	1.3030	0.9843	0.8250	0.9438
10-3	1.4093	1.2579	0.8778	1.1492
10-4	1.3925	1.3570	1.1951	1.3650
10-5	1.4025	1.2937	1.3477	1.3464
20-1	0.9197	0.7096	0.7964	1.0068
20-2	1.1472	1.2050	0.9931	1.0427
20-3	1.3364	1.1906	1.2840	1.2272
20-4	1.3118	1.2774	1.4489	1.3288
20-5	1.3075	1.3929	1.5299	1.5478
30-1	0.9893	0.8352	1.1359	0.7638
30-2	1.2682	1.2914	1.2020	1.0656
30-3	1.4657	1.2368	1.4348	1.1991
30-4	1.4486	1.3500	1.3806	1.4974
30-5	1.6543	1.5528	1.6853	1.5163

polar planimeter, and the areas in square centimeters are shown in Tables VI to IX.

The sulfamerazine suspension systems evaluated are listed in Tables VI and VII. The suspension systems shown in Table VII indicate considerable thixotropy (when polyethylene glycol is present with CMHEC 43L 4%); and when compared to the control (CMHEC 43L 4%), the suspension systems also had high  $N$  and  $\eta'$  values, an indication of the marked influence of the polyethylene glycol present in the system. The systems evaluated and shown in Table VI show greater  $N$  and  $\eta'$  values when the lower molecular weight polyethylene glycols are used. A comparison of the control system to the combination systems again shows the same trends observed with the 4% systems—namely, lower  $\eta'$ ,  $N$ , and thixotropic areas than the combination systems.

The zinc oxide systems evaluated are presented in Tables VIII and IX. Considerable thixotropy, indicated by the thixotropic areas, was observed again with the higher concentration of CMHEC 43L and polyethylene glycol. Considerable variation in both  $\eta'$  and  $N$  in the 2% CMHEC 43L combination systems (Table VIII) was noted. However, the control sample of the 4% CMHEC 43L series showed

lower  $N$  and  $\eta'$  values when compared to the combination systems, again indicating the importance of the presence of polyethylene glycol in these suspension systems.

The general trends observed in the suspension systems evaluated are that when the interacted CMHEC 43L-polyethylene glycol systems are employed as suspending vehicles, pronounced rheological effects are noted. The changes in these systems, observed by increased  $\eta'$  and thixotropic area values, are not necessarily solely a function of the insolubles present but may be due to a combined effect of the interacted polymeric system and the insoluble medicament. This specific observation may be more readily apparent when the data of the control systems are observed in Tables VI to IX. Generally, it may be observed that these effects are more readily noted when the lower molecular weights of polyethylene glycol are used in the combination systems.

#### Sedimentation Study of the Suspension Systems.

—A settling rate study was conducted on each of the suspension samples rheologically evaluated. Observations were made at intervals over a 120-day period. The schematic representation of the find-

TABLE VI.—10% SULFAMERAZINE CALCOMITES SUSPENSIONS IN VEHICLES OF 2% CMHEC 43L AND VARIOUS MOLECULAR WEIGHT POLYETHYLENE GLYCOLS<sup>a</sup>

$\bar{M}$ PEG	5%			Polyethylene Glycol, Conc.			20%		
	$\eta'$	$N$	Thix. Area	$\eta'$	$N$	Thix. Area	$\eta'$	$N$	Thix. Area
200	1341.28	1.3847	<i>b</i>	816.17	1.3305	<i>b</i>	249.59	1.1893	<i>b</i>
300	...	...	...	3926.13	1.5079	<i>b</i>	...	...	...
400	139.86	1.1343	<i>b</i>	99.64	1.1059	1.5	519.73	1.2720	0.88
600	...	...	...	531.51	1.2690	<i>b</i>	...	...	...
1000	...	...	...	79.66	1.0775	2.15	...	...	...
4000	17.73	0.9098	<i>b</i>	233.48	1.1946	2.81	104.03	1.1946	5.07
6000	...	...	...	139.80	1.1261	3.85	...	...	...
9000	...	...	...	564.33	0.9549	6.70	...	...	...
Control <sup>c</sup>	25.55	0.9549	<i>b</i>	...	...	...	...	...	...

<sup>a</sup>  $\eta'$  values,  $N$  values, and thixotropic areas in square centimeters. <sup>b</sup> Thixotropic areas are negligible and could not be determined accurately. <sup>c</sup> Contained 2% CMHEC 43L and 10% sulfamerazine calcomites.

TABLE VII.—10% SULFAMERAZINE CALCOMITES SUSPENSIONS IN VEHICLES OF 4% CMHEC 43L AND VARIOUS MOLECULAR WEIGHT POLYETHYLENE GLYCOLS<sup>a</sup>

$\bar{M}$ PEG	5%			Polyethylene Glycol, Conc.			20%		
	$\eta'$	$N$	Thix. Area	$\eta'$	$N$	Thix. Area	$\eta'$	$N$	Thix. Area
200	2375.34	1.4351	10.40	1262.47	1.3759	11.50	3,445.61	1.3759	12.17
300	...	...	...	1097.54	1.3561	10.10	...	...	...
400	4553.62	1.4972	12.70	868.13	1.3350	12.73	53,609.48	1.5250	26.80
600	...	...	...	1850.06	1.4077	13.71	...	...	...
1000	...	...	...	1615.35	1.3926	17.21	...	...	...
4000	2956.50	1.4643	11.40	1454.75	1.3883	15.75	4,345.08	1.3883	29.50
6000	...	...	...	1275.81	1.4036	16.67	...	...	...
9000	...	...	...	970.81	1.3388	13.10	...	...	...
Control	307.59	1.2114	5.26	...	...	...	...	...	...

<sup>a</sup>  $\eta'$  values,  $N$  values, and thixotropic areas in square centimeters.

TABLE VIII.—10% ZINC OXIDE SUSPENSIONS IN VEHICLES OF 2% CMHEC 43L AND VARIOUS MOLECULAR WEIGHT POLYETHYLENE GLYCOLS<sup>a</sup>

$\bar{M}$ PEG	5%		Polyethylene Glycol, Conc.		20%	
	$\eta'$	$N$	$\eta'$	$N$	$\eta'$	$N$
200	13.5	0.8543	278.51	1.2091	1097.91	1.3582
300	...	...	17.32	0.9122	...	...
400	10.19	0.8606	11.09	0.8560	66.61	1.0571
600	64.46	1.0623	185.55	1.1728	222.06	1.1561
1000	...	...	88.35	1.0921	...	...
4000	111.49	1.1229	55.58	1.0349	2581.05	1.4494
6000	...	...	38.78	0.9922	...	...
9000	...	...	357.44	1.0991	...	...
Control	141.08	1.0927	...	...	...	...

<sup>a</sup>  $\eta'$  values,  $N$  values, and thixotropic areas in square centimeters. Thixotropic areas are negligible and could not be determined accurately.

TABLE IX.—10% ZINC OXIDE SUSPENSIONS IN VEHICLES OF 4% CMHEC 43L AND VARIOUS MOLECULAR WEIGHT POLYETHYLENE GLYCOLS<sup>a</sup>

$\bar{M}$ PEG	5%			Polyethylene Glycol, Conc.			20%		
	$\eta'$	$N$	Thix. Area	$\eta'$	$N$	Thix. Area	$\eta'$	$N$	Thix. Area
200	1731.69	1.3948	5.47	2235.80	1.4357	6.10	3206.70	1.4705	15.85
300	...	...	...	1682.46	1.4009	8.43	...	...	...
400	1365.70	1.3810	6.54	1376.71	1.3809	9.56	7104.95	1.5586	20.46
600	876.92	1.3287	6.85	1253.89	1.3524	8.30	8225.90	1.5581	16.08
1000	...	...	...	2607.80	1.4469	10.66	...	...	...
4000	631.04	1.2929	6.70	2398.71	1.4350	11.70	5428.15	1.5160	20.90
6000	...	...	...	4083.46	1.5013	12.62	...	...	...
9000	...	...	...	2828.66	1.4490	13.01	...	...	...
Control	717.11	1.2737	4.60	...	...	...	...	...	...

<sup>a</sup>  $\eta'$  values,  $N$  values, and thixotropic areas in square centimeters.

ings is presented in Fig. 1. The height of the original sample ( $H_o$ ) and the height of the settled phase ( $H_u$ ) were noted; the ratio  $H_u/H_o$  was cal-

culated and plotted as shown in Fig. 1. The data are presented in the manner according to the literature (2, 34) which best represents the trends shown.

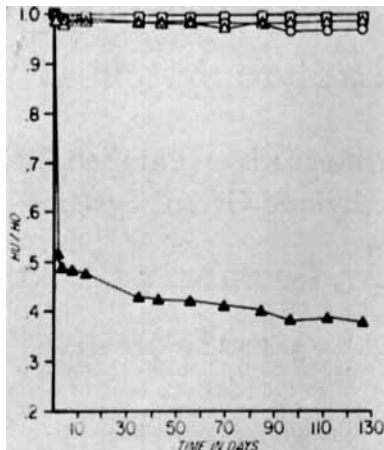


Fig. 1.—Settling rate observations of the control suspension systems.  $H_u$  = ultimate suspension height and  $H_o$  = original suspension height. Key:  $\square$ , 4% CMHEC 43L ZnO 10% and 4% CMHEC 43L sulfamerazine 10%;  $\Delta$ , 2% CMHEC 43L ZnO 10%;  $\circ$ , 2% CMHEC 43L ZnO 10%;  $\blacktriangle$ , 2% CMHEC 43L sulfamerazine 10% (cake).

The 4% CMHEC control systems of zinc oxide or sulfamerazine showed absence of caking and little phase separation. The term "phase separation" describes the clear supernatant layer forming above the suspension system. Some of the sulfamerazine systems prepared with 4% CMHEC 43L and polyethylene glycol showed signs of separation (striation) after 120 days of observation.

In the 2% CMHEC 43L control systems, no caking and little phase separation was observed in the zinc oxide systems; however, sulfamerazine showed considerable caking and slight phase separation. Some of the CMHEC 43L-sulfamerazine-polyethylene glycol systems showed striation or fissuring after 100 days of observation. It is believed that the striation of these suspension systems is not detrimental since they may be redispersed readily upon agitation, particularly when the low concentration of CMHEC 43L is present.

Analogous to the trends noted in the rheological evaluation of these suspension systems (Tables VI to IX), the phase separation of the respective suspension systems was slight when CMHEC 43L and polyethylene glycol vehicles were used. The phase separation was observed to be equally small when both the higher and lower concentrations of CMHEC 43L were used in the system. Because of this observation, the data for the CMHEC-polyethylene glycol-zinc oxide or sulfamerazine suspension systems are not given, but the systems are described in Fig. 1. Therefore, it may be stated from the trends shown that good stabilizing effects are achieved when a combination of CMHEC 43L and polyethylene glycol is used in suspensions of the insoluble medicaments considered.

## CONCLUSIONS

A computer program was written for the IBM 7090/1401 computer system using Fortran for the power law equation  $\eta' = F^N/G$ .

CMHEC 43L and CMHEC 37L were evaluated in combination with the polyethylene glycols with a molecular weight range of 200 to 9000. Large increases in  $\eta'$  (indicator of viscosity), using the power law equation for the evaluation of the rheograms, were obtained predominantly with CMHEC 43L and low molecular weight polyethylene glycols. Small changes in  $N$  of the power law equation produce an exaggerated change in  $\eta'$ . The down curve data of the rheograms were evaluated. Superior suspension stability was observed when systems were prepared containing 10% of either zinc oxide or sulfamerazine in a selected number of CMHEC 43L-polyethylene glycol systems. These systems showed no caking and little phase separation in the 120-day observation period. The use of intermediate concentrations of both CMHEC 43L and polyethylene glycol is necessary to avoid undue thixotropy as a result of the enhanced viscosity obtained with these systems. A cellulose polymer (CMHEC 43L) has been interacted with a series of polyhydroxyl compounds (polyethylene glycol), resulting in an increased pseudoplastic viscosity ( $\eta'$ ) permitting stabilization of the suspension systems studied through flocculation and/or rheological control or both flocculation and rheological control.

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