

## AREA UNDER RHEOGRAM AS MULTI-POINT VISCOSITY CHARACTERISTIC OF THE STERILIZED HYPROMELLOSE HYDROGELS

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**Abstract:** In this work, the cone and plate rheological viscometry readings of the sterilized hydrogels of hypromellose 4000 (60 g/L) were investigated by using of the three-parameter Herschel and Bulkley power law and the new empirical two-parameter model. In it, the independent variable of shear rate was transformed by logarithm and the dependent variable of shear stress by square root. The two-parameter model showed only non-significantly lower mean value of the coefficient of determination when compared with the results of the three-parameter power law model being of good promise in other investigation of the near pseudoplastic rheograms of hypromellose hydrogels. To express the influence of the addition of the isotonic concentration of sodium chloride and/or pilocarpine hydrochloride, respectively, on the viscosity of sterilized hydrogels of hypromellose, the area under rheogram (AUR) data was employed as a multi-point rheological characteristic. No significant differences were noted between AUR calculated using three parameters of the power law model and those calculated using two parameters of the proposed one. The significant increase in viscosity was observed in the presence of the isotonic concentration of sodium chloride in comparison to the hydrogel without additives. In the opposite, the addition of the isotonic concentration of pilocarpine hydrochloride resulted in the significant viscosity decrease. In conclusion, the proposed empirical two-parameter model could be used as the rheological model in investigation of the near pseudoplastic rheograms of the sterilized hypromellose hydrogels.

**Keywords:** area under rheogram, hydrogels, hypromellose, viscosity

Viscosity-increasing agents are extensively used in the formulation of many pharmaceuticals. In the liquid and hydrogel formulations, cellulose derivatives are used most frequently. As increased viscosity can offer both advantages and disadvantages with respect to use of the preparation, therefore, knowledge of viscosity and flow properties is important to the pharmacist in selecting appropriate ingredients. If sterility of the preparation is required, the alteration in viscosity properties due to the sterilization process and various additives, namely electrolytes, should be investigated.

Wide differences in the rheological behavior of polymers have been detected. In order to describe the flow behavior of the plastic samples, such as for example hydrogels, the power law function of Herschel and Bulkley could obviously be employed (1):

$$\tau = \tau_0 + k \cdot D^n \quad (1)$$

with independent variable of shear rate  $D$  ( $s^{-1}$ ) and dependent variable of shear stress  $\tau$  (Pa). This rheo-

logical model uses three parameters: consistency factor  $k$  ( $Pa \times s^n$ ), model flow behavior index  $n$  (dimensionless), and yield stress  $\tau_0$  (Pa). As  $\tau_0 \neq 0$ , the equation 1 doesn't start from the ordinate origin. However, the direct comparison of parameter triplets is difficult when the viscosity changes are investigated.

To compare viscosity measurement results, the apparent viscosity is generally referred to wherever the rheograms start from the ordinate origin, such as in the case of the pseudoplastic samples. It is usually read as the ratio of the shear stress measured and the shear rate chosen, regardless of the actual slope of the rheogram at this point (2). Commonly, shear rate equal to  $100 \text{ s}^{-1}$  ( $D_{100}$ ) is used.

As previously proposed by Marquardt and Sucker (3), common rotational viscometry readings could also be reduced to area under rheogram data (AUR) by integration. Generally, the definite integral within the range of shear rate  $D_{\min} \leq D \leq D_{\max}$  should be calculated to obtain the AUR data. Using

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three parameters of the Herschel and Bulkley power law model (equation 1), equation 2 could be generated:

$$\text{AUR} (D_{\min} - D_{\max}) = [\tau_0 (D_{\max} - D_{\min})] + k \left[ \frac{D_{\max}^{n+1} - D_{\min}^{n+1}}{n+1} \right] \quad (2)$$

The value of  $D_{\min}$  should ideally correspond to the minimal value of shear rate  $D$  at which the viscous sample starts to flow, i.e.,  $D$  for  $\tau = 0$  Pa (4).  $D_{\max}$  represents the upper limit of the definite integral. Advisably, it could be chosen in consideration to the commonly used shear rate  $D_{100}$  at which the apparent dynamic viscosity  $\eta_{100}$  is usually read.

In this methodological work, the influence of the addition of the isotonic concentration of sodium chloride and/or pilocarpine hydrochloride, respectively, on the viscosity of sterilized hydrogels of hypromellose (HPMC 4000) was investigated. To describe the rheological behavior of hydrogels, the new empirical two-parameter equation was introduced. Using its two parameters, the area under rheogram data were calculated and compared with the AUR data calculated using the three-parameters of Herschel and Bulkley model.

## MATERIALS AND METHODS

### Materials

Hypromellose (HPMC, Methocel® F4M Premium, Dow Chemical Company, USA), sodium chloride, and pilocarpine hydrochloride of pharmaceutical grade were used in this work. Water for injection was used as a solvent.

## Methods

### Preparation of hydrogels

Three groups of hydrogels with four samples in each group were prepared by stationary method (5) in which 47.0 g of water for injection and the required mass of sodium chloride (9 g/L) and/or pilocarpine hydrochloride (41 g/L), respectively, were weighed into a 100-mL autoclave bottle. After dissolving of additive and heating of solution to 90–95°C, 3.0 g of hypromellose (i.e., 60 g/L) were layered on the surface of the liquid, the bottles were closed with the rubber closure and aluminium capture and loaded into the laboratory scale autoclave immediately. After steam sterilization (at 121°C, 30 min) the pressure was returned to the atmospheric one and the bottles were left to cool slowly to room temperature inside the autoclave chamber. To obtain the gels of great clarity, the bottles were then stored in the refrigerator at 4°C for four weeks. This way all samples of hydrogel were prepared. The sterilized hydrogel without additives was prepared the same way and used as a control for the investigation of viscosity changes.

### Measurement of viscosity

Viscosity of all hydrogel samples was measured using cone and plate rotational viscometer Rheotest 2 (Mechanik Prüfgeräte, Medingen, Germany). The cone K1 with the diameter of 36 mm and the aperture angle between cone and plate of 0.3° was used. Before the viscosity measurement, the sample of hydrogel was placed on a thermostated ( $32 \pm 0.1^\circ\text{C}$ ) viscometer plate for 30 min to reach

Table 1. Rotational viscometry readings of sterilized hydrogels of hypromellose.

Additive	Shear stress $\tau$ (Pa)					
	11 s <sup>-1</sup>	20 s <sup>-1</sup>	33 s <sup>-1</sup>	60 s <sup>-1</sup>	100 s <sup>-1</sup>	180 s <sup>-1</sup>
None	190	313	448	626	760	931
	192	328	458	628	769	946
	198	336	460	632	780	977
	206	343	466	634	794	992
Sodium chloride (9 g/L)	275	375	492	646	812	988
	290	394	516	683	820	1001
	292	408	520	696	843	1026
	293	410	535	705	861	1057
Pilocarpine hydrochloride (41 g/L)	148	241	361	533	694	843
	153	248	372	545	717	879
	158	261	394	570	723	898
	177	285	4520	599	752	932

the temperature equilibrium. Each hydrogel sample was measured five times at shear rates  $D$  equal to 11, 20, 33, 60, 100, and 180  $s^{-1}$ . All hydrogels showed near pseudoplastic flow behavior. Mean values ( $n = 5$ ) of measured shear stress  $\tau$  in Pa, which relative standard deviation was lower than 5%, were used for hydrogel characterization. Results of the rheological readings are presented in Table 1.

### Rheological model

Providing the appropriate transformation of variables, the empirical two-parameter equation 3 was proposed:

$$\sqrt{\tau} = a + (b \cdot (\ln D)) \quad (3)$$

where variables  $\tau$  and  $D$  are as defined above, and  $a$  and  $b$  are parameters of the equation. The area under rheogram is then calculated by the squaring of equation 3 as follows:

$$\begin{aligned} \text{AUR} (D_{\min} - D_{\max}) = & a^2 [(D_{\max} - D_{\min})] + \\ & + ab[(-2D_{\min} \cdot \ln D_{\min}) + 2D_{\min} + (2D_{\max} \cdot \ln D_{\max}) - \\ & - 2D_{\max}] + b[(-D_{\min} \cdot \ln D_{\min}^2) + (2D_{\min} \cdot \ln D_{\min}) - \\ & - 2D_{\min} + (D_{\max} \cdot \ln D_{\max}^2) - (2D_{\max} \cdot \ln D_{\max}) + \\ & + 2D_{\max}] \end{aligned} \quad (4)$$

## RESULTS AND DISCUSSION

### Rheological model

Rheological behavior and intimate characterization of flow properties is relevant for product reliability and quality control. To describe the flow properties of the various samples, many rheological models were examined (1, 2). Mean values of the shear stress obtained for four samples of each out of

three hydrogel groups studied, listed in Table 1, were modelled using the three-parameter power law (equation 1). The parameters of the model are summarized in left part of Table 2 together with the coefficient of determination  $r^2$ . The mean value of the coefficient of determination equal to 0.9987 proved the suitability of the implementation of the parameter  $\tau_0$  in equation 1 and the use of the three-parameter power law model for investigation of the samples. The estimated yield stress values  $t_0$  have a negative sign because they express the value, where the rheogram, with independent variable of shear rate and dependent variable of shear stress, appears to intersect the stress axis. It could be noted that the estimation of the parameter triplets is fairly difficult. Moreover, the direct comparison of parameter triplets is not very illustrative due to the very low values of the exponent  $n$  and the values of parameter  $k$ , which are located near the ordinate origin where they have no physical explication.

The rheological data (Table 1) were also modelled with the proposed empirical two-parameter equation 3. In this equation, the variables were transformed by similar way as used successfully in the previously studied relationship between the logarithm of viscosity and the square root of the concentration of aqueous solution of cellulose derivatives (6). The values of parameter  $a$ , representing an intercept, and  $b$ , representing a slope, are summarized in right part of Table 2 together with the coefficients of determination  $r^2$  again.

As could be seen from Table 2, only non-significantly lower mean value of the coefficient of

Table 2. Comparison of parameters of the equation 1 and equation 3.

Additive	Equation 1				Equation 3		
	k	n	$-\tau_0$	$r^2$	a	b	$r^2$
None	1654	0.108	1959	0.9988	-0.30	6.04	0.9952
	1632	0.109	1932	0.9998	-0.09	6.03	0.9955
	915	0.163	1154	0.9999	-0.15	6.11	0.9978
	738	0.186	947	0.9999	0.07	6.10	0.9987
Sodium chloride (9 g/L)	321	0.277	352	0.9990	3.40	5.40	0.9989
	537	0.212	608	0.9989	4.21	5.30	0.9991
	519	0.220	590	0.9992	4.08	5.40	0.9995
	507	0.227	583	0.9997	3.75	5.55	0.9998
Pilocarpine hydrochloride (41 g/L)	443	0.235	640	0.9962	-2.79	6.23	0.9965
	368	0.264	549	0.9968	-2.97	6.36	0.9974
	601	0.205	833	0.9979	-2.55	6.35	0.9973
	662	0.196	890	0.9982	-1.63	6.27	0.9976

determination was noted when compared with the results of the three-parameter equation 1. A couple of parameters, moreover, varied much lower than the triplet of parameters of equation 1. Making a comparison between the negative yield values  $\tau_0$  of the Herschel and Bulkley power law and the negative values of the parameter  $a$  of the proposed two-parameter equation 3 for shear rate  $D = 1 \text{ s}^{-1}$  (discussed later), decimal reduction in the values was detected for the parameter  $a$ . The very small differences between values were observed for the parameter  $b$  in contrast to the parameter  $a$  with the more fluctuated values. Therefore, it was concluded that equation 3 seemed to be appropriate in other investigation of the near pseudoplastic rheograms of hypromellose.

#### Area under rheogram

To characterize data of various rotational viscometer readings, a method in which rheogram data were changed to area under rheogram (AUR) data by integration was referred for the emulsion gels (3). In order to obtain the precise AUR data, the estimation of both the lower ( $D_{\min}$ ) and the upper limit ( $D_{\max}$ ) of the definite integral are important. In this work, the upper limit of integration was chosen in reflect to the conventional shear rate at which the apparent viscosity is read, i. e.,  $D_{\max} = 100 \text{ s}^{-1}$ . For the plastic samples, the  $D_{\min}$  should optimally correspond to such value of shear rate at which the sample just starts to flow, i. e.,  $D_0$  for  $\tau = 0 \text{ Pa}$ . The value

of  $D_0$  cannot be determined directly from the plastic rheogram but it can be calculated using three parameters of equation 1 (4):

$$D_0 = \sqrt[3]{\frac{-\tau_0}{k}} \quad (5)$$

Using equation 5,  $D_0$  values were calculated for all samples of three hydrogel groups investigated. Results are shown in the left part of Table 3 together with the values of AUR ( $D_0 - 100$ ) calculated by equation 2 within the range of shear rate  $D_0 = D = D_{100}$ . Although the estimated values of AUR provide the highest level of accuracy, on the other hand, the empirical determination of the  $D_0$  value by iteration is time consuming being associated with searching of the maximum value of the coefficient of determination.

Due to the appropriate mathematical manipulation of variables, the empirical two-parameter equation 3 was proposed in this work to describe rheological behavior of the sterilized hydrogels of hypromellose. This manner, the generated two-parameter linear regression allows to calculate the AUR data as the area of the rectangular triangle. However, the used logarithmical transformation of shear rate necessitates to locate the lower limit of calculation ( $D_{\min}$ ) to  $D = 1 \text{ s}^{-1}$  as the logarithm of zero is mathematically undefined. Thus, the transformed value of  $D$  will be equal to zero ( $\ln 1 = 0$ ) leading to the important simplification of the equation 4 as follows:

$$AUR (1 - 100) = 99a^2 + 723ab + 1398b^2 \quad (6)$$

Table 3. Comparison of area under rheogram (AUR, in  $\text{kPa}\cdot\text{s}^{-1}$ ) calculated using equation 2 and equation 6.

Additive	Equation 2		Equation 6
	$D_0$ ( $\text{s}^{-1}$ )	AUR ( $D_0-100$ )	AUR (1-100)
None	4.8	50.5	49.7
	4.7	50.8	50.4
	4.2	51.9	51.5
	3.8	52.4	52.3
Sodium chloride (9 g/L)	1.4	54.9	55.2
	1.8	57.0	57.2
	1.8	58.4	58.3
	1.9	59.4	59.5
Pilocarpine hydrochloride (41 g/L)	4.8	42.4	42.5
	4.6	43.8	43.8
	4.9	45.6	45.3
	4.5	48.2	47.8
Mean	3.60	51.28	51.13

In right part of Table 3, the resulting values of AUR (1–100) are summarized.

The mean values of AUR acquired by using both rheological models (equation 2 and equation 6) are compared in the last row of Table 3. As could be seen, the very similar AUR data were noted with the differences resulting only from the rounding of the values. Therefore, the obtained values of AUR (1–100) were used to express the influence of electrolyte additives on the viscosity of sterilized HPMC hydrogels.

The mean AUR data of the quaternion of the hydrogel samples of the three hydrogel groups were studied using Scheffe's method for comparing the pairs of means. Both studied electrolyte additives changed the viscosity of sterilized HPMC hydrogels significantly ( $p = 0.01$ ). While the addition of the isotonic concentration of sodium chloride increased the viscosity of hydrogel in comparison with the hydrogel without additives, the addition of the isotonic concentration of pilocarpine hydrochloride, in contrast, resulted in the viscosity decrease. The lower viscosity of pilocarpine hydrogel samples could be seen simply by eye when tilting the autoclave bottle.

## CONCLUSIONS

Hypromellose is widely used in many pharmaceutical preparations. Wherever sterility is required, one of the major problems is that both sterilization process and additives could affect the polymer viscosity. In addition to the three-parameter power law model, in this work, cone and plate viscometry readings were modelled by the new empirical two-parameter equation in which rheological variables: the shear rate and the shear stress were appropriately transformed. Based on the results, the proposed equation has been found to be a suitable rheological model to study the near pseudoplastic rheograms of the sterilized hypromellose hydrogels. In order to

investigate the influence of the addition of isotonic concentration of sodium chloride and/or pilocarpine hydrochloride, respectively, on the viscosity of sterilized hydrogel, the area under rheogram (AUR) data were employed. Using two parameters of the proposed equation 3, this multi-point rheological characteristic was calculated in the range of  $1 = D = 100 \text{ s}^{-1}$ . In comparison to the sterilized HPMC hydrogels without additives, viscosity was significantly increased in the presence of isotonic concentration of sodium chloride while the significant opposite effect was observed in the presence of isotonic concentration of pilocarpine hydrochloride. Finally, the two-parameter equation 3 could be employed in the near pseudoplastic flow curve investigation considering the appropriate transformation of the rheological variables: the shear rate and the shear stress, and locating the lower limit of AUR data calculation to shear rate of  $1 \text{ s}^{-1}$ .

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